Pharmacist led interventions to improve medication related care of community-dwelling patients

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Volume I

Declaration

This thesis contains no material that has been accepted for the award of any other degree or diploma in any University or College.

To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except when due reference is made in the text of the thesis.

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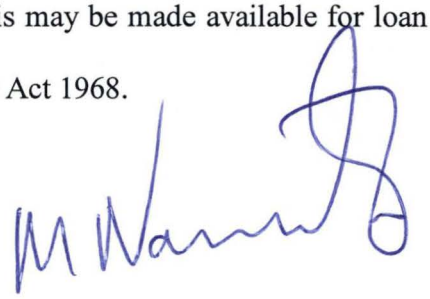

Mark Naunton

"I am not built for academic writings. Action is my domain".

Mahatama Gandhi (1869-1948)

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List of publications

Peer-reviewed journal publications

Naunton M, Peterson GM, Jones G. Addressing information needs in the management of osteoporosis. *Osteoporos Int* 2004; 15 (6): 505.

Naunton M, Peterson GM, Jones G, Griffin G, Bleasel MD. Multi-faceted educational program increases prescribing of preventive medication for corticosteroid-induced osteoporosis. *J Rheum* 2004; 31 (3): 550-56 (editorial published in same issue as a result of this research).

Naunton M, Peterson GM. Home-based clinical pharmacy follow-up of 'high risk' patients discharged from hospital. *J Pharm Pract Res* 2003; 33: 176-82.

Professional journal publications

Peterson GM, Naunton M. Provision of samples: help or hindrance in the elderly. *Aust Pharmacist* 2003; 22: 528-30.

Peterson GM, Naunton M, Fitzmaurice K. The drugs could be OK, but don't forget problems with dosage forms in the elderly. *Aust Pharmacist* 2003; 22: 212-15.

Peterson GM, Jackson SL, Naunton M. Communication problems in the elderly can lead to disasters: Chaos theory in action. *Aust Pharmacist* 2003; 22: 49-51.

Peterson GM, Naunton M. Simple measures to assist with drug therapy can produce large benefits for elderly patients. *Aust Pharmacist* 2002; 21: 370-73.

Naunton M, Peterson GM, Griffin G. Corticosteroid-induced osteoporosis – pharmacists well placed to assist. *Aust Pharmacist* 2002; 21: 27-29.

Manuscripts in preparation

Naunton M, Peterson GM, Jones G. Use of quantitative heel ultrasound to screen elderly rural women in community pharmacies for osteoporosis. *J Clin Densitom.*

Naunton M, Peterson GM, Jones G. Calcium intake among rural elderly Australian women presenting to community pharmacies. *Aust J Rural Health.*

Naunton M, Peterson GM, Jones G. Lack of treatment with bisphosphonates in subjects with prior low-trauma fracture presenting to community pharmacy for osteoporosis screening. *Osteoporos Int.*

Naunton M, Peterson GM. Cost-benefit analysis of a pharmacist conducted home-visit in patients recently discharged from hospital. *Br J Clin Pharm.*

Conference abstracts (oral)

Naunton M, Peterson GM, Jones G. Tackling osteoporosis in a rural-based population. Society of Hospital Pharmacists of Australia (Tasmanian State Conference), Cradle Mountain, March 19-21, 2004.

Jones G, Naunton M, Peterson GM. Osteoporosis treatment gaps. Advanced Trainee Weekend. Gold Coast, Qld, March 20-21 2004. (research presented by Associate Professor Graeme Jones).

Naunton M, Peterson GM. Importance of hospital pharmacist involvement in the provision of home medication reviews following hospitalisation of "high-risk" patients. Society of Hospital Pharmacists of Australia, Federal Conference, Canberra, ACT, November 13-16, 2003.

Naunton M, Peterson GM, Jones G, Griffin G, Bleasel MD. Pharmacist-led academic detailing increases the use of preventive medication in patients prescribed long-term corticosteroids. The Royal Australian College of General Practitioners 46th National Convention & Annual General Meeting (RACGP AGM), Hobart, Tasmania, October 5-10, 2003.

Naunton M, Peterson GM. Home-based clinical pharmacy follow-up of 'high risk' patients discharged from hospital. Australian Resource Centre for Hospital Innovations (ARCHI), Adelaide, South Australia, June 26-27, 2003.

Naunton M, Peterson G, Jones G, Griffin G, Bleasel MD. Multi-faceted educational program increases prescribing of preventive therapy against corticosteroid-induced osteoporosis. Society of Hospital Pharmacists of Australia State Conference, Strahan, Tasmania, March 21-23, 2003 (awarded best paper).

Naunton M, Peterson GM, Jones G, Griffin G, Bleasel MD. Multi-faceted educational program increases prescribing of preventive therapy against corticosteroid-induced osteoporosis. 3rd International Congress on Glucocorticosteroid Induced Osteoporosis, Turin, Italy, March 6-8, 2003.

Naunton M, Peterson GM, Griffin G, Jones G, Bleasel MD. Multifaceted method to promote preventive therapy against corticosteroid-induced osteoporosis. Pharmacy Australia Congress (PAC), Hobart, Tasmania, October 18-21, 2002.

Naunton M, Peterson GM. Home-based clinical pharmacy follow-up of 'high risk' patients discharged from hospital. Australasian Pharmaceutical Science Association (APSA), Melbourne, Victoria, December 7-11, 2002.

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Naunton M, Peterson GM, Vial, J. Evaluation of home-based clinical pharmacy follow-up of 'high risk' patients discharged from hospital. Society of Hospital Pharmacists of Australia, Federal Conference, Hobart, Tasmania, November 8-11, 2001.

Conference abstracts (poster)

Naunton M, Peterson GM, Jones G. Evaluation of pharmacist performing osteoporosis screening in rural pharmacies using quantitative heel ultrasound (QUS). 33rd European Symposium on Clinical Pharmacy, Prague, Czech Republic, October 20-24, 2004.

Naunton M, Peterson GM, Jones G. Evaluation of pharmacist performing osteoporosis screening in rural pharmacies using quantitative heel ultrasound (QUS). Australian and New Zealand Bone Mineral Society Annual Scientific Meeting, Hunter Valley, NSW, Australia, August 18-20, 2004.

Naunton M, Peterson GM, Griffin G, Jones G, Bleasel MD. Multi-faceted educational program increases prescribing of preventive medication against corticosteroid-induced osteoporosis. 63rd FIP Pharmacy World Congress, Sydney, NSW, September 4-9, 2003.

Naunton M, Jackson SL, Peterson GM. An educational model using hospital-based guidelines and data to improve the prescribing of preventive medicines for chronic conditions. Society of Hospital Pharmacists of Australia, Federal Conference, Canberra, November 13-16, 2003.

Naunton M, Peterson GM, Griffin G, Jones G, Bleasel MD. Multifaceted method to promote preventive therapy against corticosteroid-induced osteoporosis. Australasian Pharmaceutical Science Association (APSA), Melbourne, Victoria, December 7-11, 2002.

All publications listed resulted from work described in this thesis.

Abbreviations

BMD = bone mineral density

BUA = broadband ultrasound attenuation

DEXA = dual X-ray absorptiometry

GP = general practitioner

HRT = hormone replacement therapy

MW U = Mann-Whitney U test

PTH = parathyroid hormone

QUM = quality use of medicines

QUS = quantitative ultrasound

SD = standard deviation(s)

SOS = speed of sound

$\chi 2$ = chi-square test

Abstract

The aim of this thesis was to demonstrate the important roles pharmacists could fulfil in improving the medication management of patients, particularly the elderly. There were three separate parts completed.

Part I

Medication mishaps and adverse events in patients post-discharge from hospital have been well established. The first part of the research evaluated a pharmacist-conducted follow-up at home of elderly patients discharged from hospital. This was a randomised controlled study of 121 "high-risk" medical patients who were assigned to an intervention or control group. A pharmacist visited the intervention patients 5 days post-discharge. The pharmacist educated patients on their medications, encouraged compliance, assessed for drug related problems, intervened where appropriate and communicated all relevant findings to community health professionals.

Intervention patients had significantly less medication-related problems at 90 days post-discharge (median 1.0) compared to control patients (median 2.0). In addition, there was an improvement in compliance, and decline in use of non-steroidal anti-inflammatory drugs. Forty-five per cent of control patients had unplanned readmissions to hospital during 90 days following discharge, compared to 28% of the intervention group patients ($p = 0.05$).

The project demonstrated that a pharmacist-conducted follow-up of "high-risk" elderly patients discharged from home is valuable in identifying and addressing drug-related problems and reducing the risk of readmission to hospital.

Part IIa

There has been much evidence published demonstrating that many women are not investigated for osteoporosis and many with osteoporosis and osteoporotic fractures do not receive adequate treatment. Quantitative heel ultrasound is recognised as a useful method for predicting risk of fracture in elderly women. Rural communities often have difficulties accessing a number of health resources including diagnostic equipment for osteoporosis. The aim of Part IIa of the thesis was to assess the role of a pharmacist, trained in the use of a portable heel ultrasound device, in screening elderly rural women for risk of osteoporosis, and assess whether those found to be at risk seek further help and treatment from their GP following the screening. In addition, the project aimed to increase the women's knowledge on osteoporosis.

Three hundred and forty-five women were recruited from 6 rural community pharmacies and underwent screening. Women were comprehensively educated on risk factors for osteoporosis and completed a calcium intake questionnaire to assess their calcium status. Results were promptly forwarded to each woman's GP and the subjects were followed-up 3 months later to assess outcomes from the screening procedure. Pharmacists and GPs were surveyed to assess their opinion.

Approximately 20% of women were shown to be at high-risk for osteoporosis and 27% of patients at increased risk for fracture. One hundred and ninety-one subjects (55%) were referred to their GP for further assessment. Sixty-eight per cent of women screened discussed their results with their doctor. Eleven per cent of women underwent further investigations and 4% had further investigations planned. Over one-third (30% calcium, 6% bisphosphonate, 6% vitamin D) of women screened commenced medication to treat or prevent osteoporosis. Two thirds of women indicated they had made lifestyle changes (e.g. increased calcium intake and exercise) following the

screening. Women's knowledge about osteoporosis increased from a median of 10/17 to 14/17 following the screening.

In conclusion, screening for osteoporosis in community pharmacies, particularly rural pharmacies, is a potentially useful method to identify women at risk for future fracture and is a suitable location for the discussion of preventive therapy. The osteoporosis screening was well received by the subjects and pharmacists. General practitioners were generally supportive of the project.

Part IIb

Long-term use of oral corticosteroids has been shown to increase the likelihood of sustaining a fracture. Guidelines exist for the prevention of corticosteroid-induced osteoporosis. However, studies have consistently shown that patients prescribed long-term oral corticosteroids do not receive adequate preventive therapy against osteoporosis. The aim of Part IIb of the thesis was to perform a controlled comprehensive educational programme intended to increase the use of preventive therapy against osteoporosis in patients prescribed long-term oral corticosteroids.

The intervention was conducted in southern Tasmania, Australia, using the north of the State as a control area. The target group of all GPs and community pharmacies in southern Tasmania were sent educational material and locally produced guidelines on the prevention of corticosteroid-induced osteoporosis. A pharmacist then visited each GP and community pharmacist, and discussed the material directly with him/her. The community pharmacists were also provided with supplies of educational refrigerator magnets, intended for patients. The outcome of the programme was measured using evaluation feedback from the GPs and pharmacists, and drug utilisation data provided by (i) a series of patients presenting to hospital and taking oral corticosteroids for at least 3 consecutive months and (ii) dispensing of osteoporosis preventive therapy and

prednisolone under the Australian Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Schemes.

The educational programme was very well received by the GPs and pharmacists. Baseline data prior to the intervention demonstrated that only 31% of admitted hospital patients on long-term oral corticosteroids were receiving preventive therapy against osteoporosis. Post-intervention data showed a significant increase to 57% of patients ($p < 0.0001$). The use of bisphosphonates, calcium and vitamin D increased significantly. Pharmaceutical Benefits and Repatriation Pharmaceutical Benefits Scheme data also indicated a significant ($p < 0.01$) increase in the dispensing of osteoporosis preventive therapy in the south compared to the north of Tasmania.

A multi-faceted educational programme, incorporating academic detailing of GPs and community pharmacists, advanced the safe use of oral corticosteroid therapy, although there was still scope for improvement in the prevention of corticosteroid-induced osteoporosis.

This thesis has shown pharmacists can have a beneficial role in the medication management of community-dwelling patients through several interventions.

Table of contents

Volume I

Volume II

General introduction

Quality use of medicines and pharmaceutical care

In Australia, the quality use of medicines (QUM) is one of the central objectives of Australia's National Medicine Policy. The goal of the National Strategy for QUM is: to "optimise the use of medicines to improve outcomes for all Australians"[1]. QUM is defined as[1]

- **Judicious selection of management options**

  This means consideration of the place of medicines in treating illness and maintaining health, recognising that for the management of many disorders non-drug therapies may be the best option.

- **Appropriate choice of medicines, where a medicine is considered necessary**

  This means that, when medicines are required, selecting the best option from the range available taking into account the individual, the clinical condition, risks, benefits, dosage, length of treatment, co-morbidities, other therapies and monitoring considerations. Appropriate selection also requires a consideration of costs, both human and economic. The costs should be considered both for the individual, the community and the health care system as a whole.

- **Safe and effective use**

  This means ensuring best possible outcomes of therapy by monitoring response, minimising misuse, over-use, as well as improving the ability of all individuals to

take appropriate actions to solve medication-related problems, e.g., adverse effects and managing multiple medications.

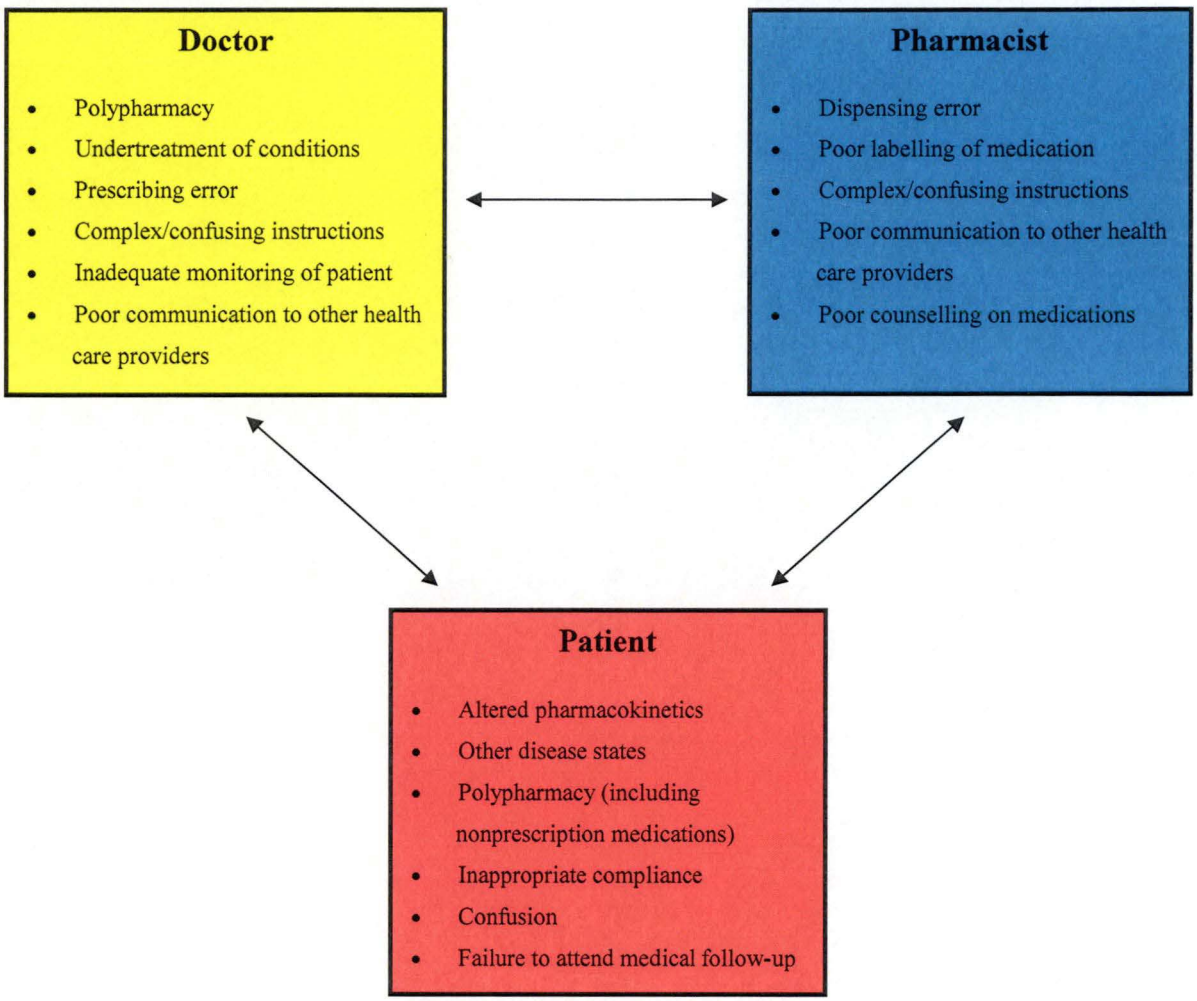
QUM, particularly in the elderly, is important to society because Australian and international reports have identified problems with medicine use amongst older people[2]. The morbidity and mortality associated with medication misadventure in Australia is also well documented[3, 4] with those over 65 years having higher medication incidents than younger people, partly because they are more likely to be taking more medications[5].

Key areas that have been identified that can contribute to problems with medications include: polypharmacy, poor communication between health care providers and patients, adverse drug events, prescribing errors, dispensing errors, poor compliance, lack of patient counselling regarding medications, and complex and confusing instructions[5].

One major contributor to inadvertent polypharmacy and drug-related problems in the elderly appears to be hospitalisation and the consequent changes in medication (drugs or brands of drugs) at the transition from out-patient to in-patient care and back[6-8]. It has been noted that the management of prescribed medications among chronically ill patients recently discharged from acute hospital care is often sub-optimal, and that an assessment of medication management in the home provides an invaluable opportunity to detect and address problems likely to result in poorer health outcomes[7, 9]. For instance, patients may be confused after discharge despite comprehensive counselling by pharmacists or other hospital staff. Improved communication between hospital and community-based health professionals is essential to enable the seamless transition of care of patients after discharge from hospital[10].

Figure 1 Examples of factors that contribute to medication problems in the elderly

(modified from Peterson[11] and the Australian Council for Safety and Quality in Health Care[5])



The goal, as always, should be to achieve safe and effective pharmacotherapy. This does not mean reducing a patient's list of medications at the expense of undertreating conditions. As noted by Beyth and Shorr[12], when used appropriately, drugs may be the single most important intervention in the care of an older patient. It is becoming increasingly recognised that undertreatment poses at least as much risk to elderly patients as polypharmacy. Many instances of underuse of appropriate drug therapy have been extensively documented. Specific examples of conditions which may

be underdiagnosed and/or undertreated, especially in elderly or socially disadvantaged patients, include:

(i) hypertension; [13-15]
(ii) hyperlipidaemia; [16-18]
(iii) congestive heart failure; [19-21]
(iv) asthma [22]
(v) depression; [23-25]
(vi) glaucoma; [26]
(vii) pain [27, 28] (partly attributable to the elderly tending to underreport their pain [29]);
(viii) acute myocardial infarction (AMI) due to the underuse of thrombolytic agents and β-blockers; [30, 31]
(ix) non-valvular atrial fibrillation (AF) due to the reluctance to use warfarin; [32-34]
(x) osteoporosis; [35-52]
(xi) postoperative venous thromboembolism due to inadequate prevention; [53, 54] and
(xii) vaccination (e.g. the underuse of influenza and pneumococcal vaccines) [55, 56].

Patient education and appropriate intervention by pharmacists are two important aspects in tackling the hazards of polypharmacy. The primary role of the pharmacist is to promote the rational and safe use of drugs. The pharmacist should regularly review the drug therapy of their elderly patients and consider whether the regimen could be simplified by (i) ceasing drugs that are either not really necessary or unlikely to significantly improve the patient's wellbeing; and (ii) replacing two or more drugs with one alternative [11]. Interventions by the pharmacist can result in significant improvements in the convenience of the drug regimen, understanding of the therapy by the patient, and patient compliance [8, 9, 57-63].

In addition, the pharmacist also has an important role in remedying undertreatment by promoting the use of medications according to evidence-based guidelines, irrespective of the age of the patient. There are also opportunities for

pharmacists to participate in disease-screenings to address the issue of underrecognition of disease and therefore attempt to correct any apparent undertreatment.

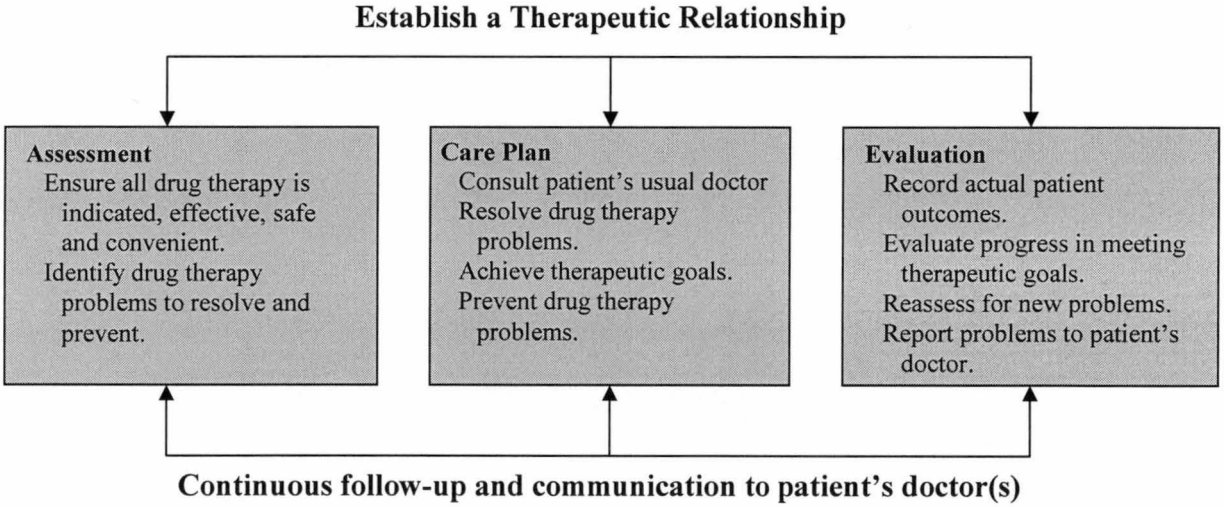
Pharmaceutical care was first defined by Mikeal *et al* [64] in 1975 as "the care that a given patient requires and receives which assures safe and rational drug usage." The definition of pharmaceutical care was further developed, and it was Hepler and Strand who re-defined pharmaceutical care as it stands today: "Pharmaceutical care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for the patient's drug-related needs"[65].

Hepler and Strand emphasised that two activities must occur for pharmaceutical care to be delivered. First, the practitioner takes time to determine the patient's specific wishes, preferences, and needs concerning his or her health and illness. Second, the practitioner makes a commitment to continue care once it is intiated[66]. It therefore followed that "pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life"[65].

Pharmaceutical care is a new philosophy of professional practice that has evolved from many years of research and practice in the profession of pharmacy. Shortly after the re-defined concept of pharmaceutical care proposed by Hepler and Strand, the theory was adapted by pharmaceutical organisations[67]. The new professional practice is not intended to replace conventional medicine (e.g., doctor), but rather meet the need of patients in a health care system that is overrun from an explosion of pharmaceuticals on the market, increased complexity of drug therapy, significant drug-related morbidity and mortality associated with drug use, and the high human and financial cost of drug misadventure[66]. The commitment to pharmaceutical care has given the opportunity for pharmacists to have new roles and responsibilities, namely to ensure the appropriate use of drug therapies to achieve desired outcomes.

Pharmaceutical care has also been described as a multi-faceted process that results in positive outcomes for the patient[68]. Associated with this process, is the delivery of appropriate pharmaceutical services, which include obtaining patient medical history, evaluating laboratory data, reviewing patient records, and performing patient counselling[68]. Because pharmaceutical services should be delivered appropriately to achieve optimal patient outcomes, research must be conducted on services that are provided.

Figure 2 The pharmaceutical care process (modified from Cipolle *et al*[69])



Pharmacists' professional services in the community setting

In Australia, community pharmacists already provide services to the elderly, such as nursing home reviews, home medication reviews, and the provision of dosage administration aids, and advise patients on a range of conditions such as asthma, diabetes, smoking cessation, wound management, cost of medication and availability of generic medications. In addition, community pharmacists distribute health information and educational material of relevance to community members and refer patients when necessary to a doctor if medical attention is required.

The value of pharmaceutical services in inpatient settings has been documented overseas[68]. Clinical pharmacy activity is prevalent in hospitals throughout Australia, although the nature and extent of services appears to be highly variable[70]. However, the value of pharmaceutical activities outside a hospital setting is less well confirmed. Certainly there is evidence that community pharmacies are providing services other than traditional dispensing of medications. For example, overseas there have been studies conducted in community pharmacies demonstrating successful interventions to control blood pressure[71-75], diabetes[76], and cholesterol[76, 77]. Furthermore, efforts in community pharmacies have demonstrated that patients can benefit from a pharmacy-conducted smoking cessation clinic[78], and weight reduction clinic[79]. Pharmacists (in parts of the United States) are also providing some vaccinations[80, 81]. Another notable clinical outcome includes improvement in compliance with medication usage[82-84].

A comprehensive review of Australian pharmacists' activities by Roughead *et al.*[85] found that there is evidence across a number of different settings for the

effectiveness of pharmaceutical care services, continuity of care services post discharge (results from Part I of thesis were included in Roughead's review), pharmacist education services to consumers and pharmacist education to health practitioners for improving patient outcomes or medication use. There is more limited evidence for the effectiveness of pharmacist managed clinics, pharmacist review of repeat prescribing and pharmacist participation in therapeutic decision making in improving patient outcomes. New professional services that have not been adequately evaluated include pharmacist administration of vaccines, pharmacist involvement in pre-admission clinics and pharmacist participation in hospital in the home services and screening for disease.

While pharmacist involvement in screening services has been examined, for example, cholesterol screening[86], the benefits to the overall health system are unclear. A critical review of the literature relating to community pharmacy involvement in health development was published in 2003 and concluded that there was insufficient evidence to determine whether screening activities in community pharmacies are an effective use of resources[87]. However, the evidence supports the wider provision of smoking cessation and lipid management through community pharmacies. Further research is needed into the contribution of community pharmacy to disease detection and case finding as part of local public health strategies[87]. There is little research that has assessed the role of pharmacist-delivered screening services on patient outcomes[85]. Australian research published by Hourihan *et al*[88] recently demonstrated that rural pharmacies can serve as a practical location to screen the public for hypertension, hyperlipidaemia and other cardiovascular disease risk factors, however other research is lacking.

Pharmacists have an integral role in the safe and effective use of medications. However, pharmacists are not yet fully integrated into the primary health care team and their skills could be better used to help patients with their long term medicines[89]. It is important that pharmaceutical services be implemented and evaluated to further establish the value of community pharmacists to the healthcare system. As noted by Rothschild *et al*:[90]

> *"Pharmacists are an underused resource for preventing medication errors. Pharmacists provide important safeguards for older patients in hospitals and nursing homes. Their roles should be expanded to other settings."*

Aims of thesis

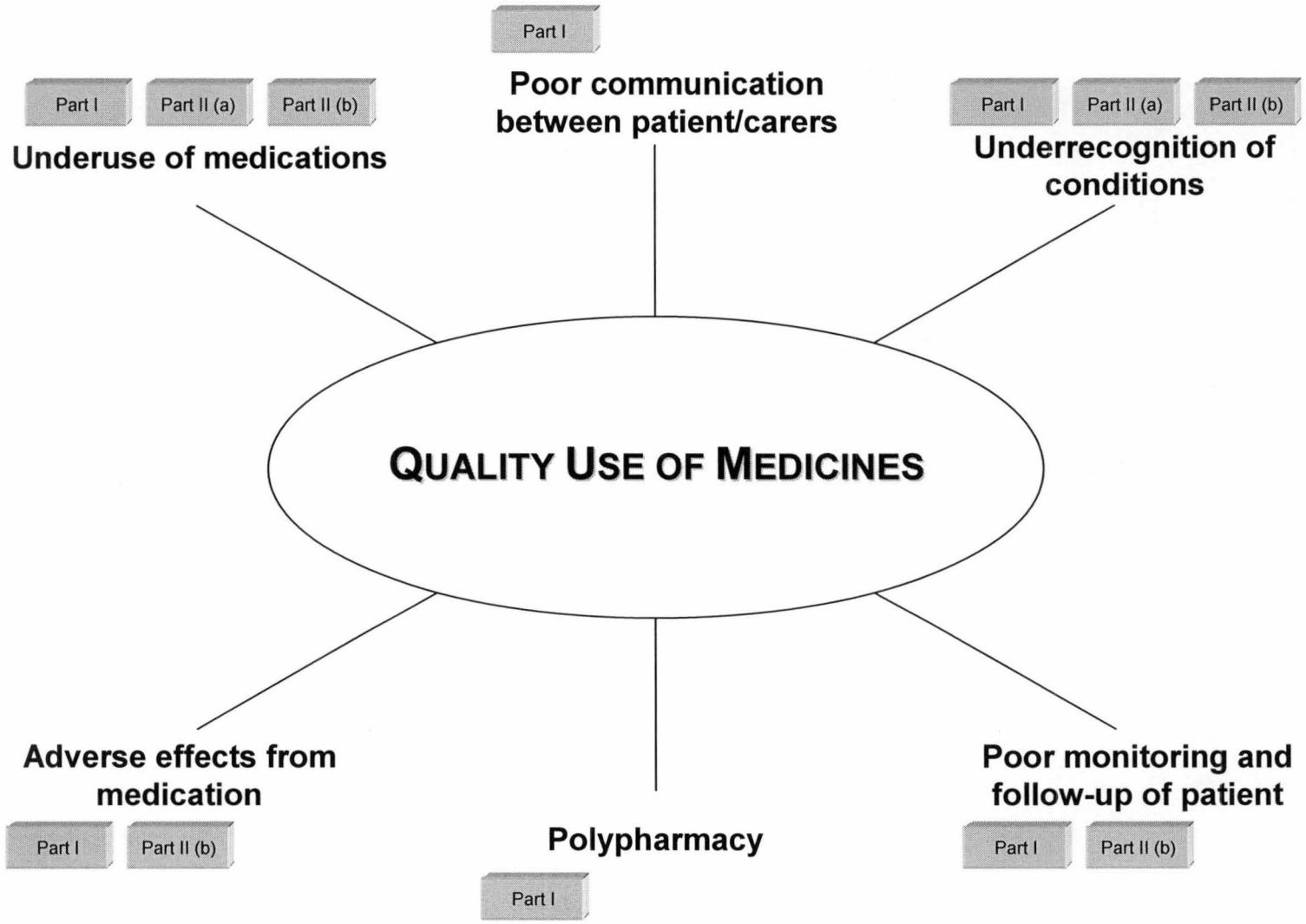
The research presented in this thesis covers three separate, but broadly related, investigations. The overall aim of the work was to implement and evaluate important roles that pharmacists could fulfil to improve the quality use of medicines in community-dwelling citizens, particularly elderly citizens.

The studies were as follows:

1. Evaluation of a pharmacist home visit following discharge from hospital in "high risk" patients.
2. Evaluation of pharmacist performing osteoporosis screening in rural pharmacies using quantitative heel ultrasound.
3. Evaluation of a multi-faceted educational programme to increase prescribing of preventive medication against corticosteroid-induced osteoporosis.

The background, methodology, results, and discussion of each study are presented separately. Figure 3 illustrates how each part presented in this thesis aimed to improve the QUM by expanding the role of pharmacists beyond dispensing and the provision of drug information in community pharmacies. This was to be achieved by firstly, addressing drug-related problems in elderly in their transition from hospital to home, secondly, improving the detection and treatment of osteoporosis by screening elderly rural women with quantitative heel ultrasound in community pharmacies and thirdly, improving the recognition and management of corticosteroid-induced osteoporosis through academic detailing.

Figure 3 Aspects of pharmacotherapy that lead to poor quality use of medicines and stages where interventions were conducted in this thesis to improve them



Part I: Evaluation of pharmacist home visit following discharge from hospital in "high risk" patients

Chapter 1: Introduction

Problems with medications and the elderly

Problems associated with the use of pharmaceutical drugs in society continue to be a significant public health burden[91]. The recently released Second National Report on Patient Safety[5] from the Australian Council for Safety and Quality in Health Care ('Improving Medication Safety') concluded the following:

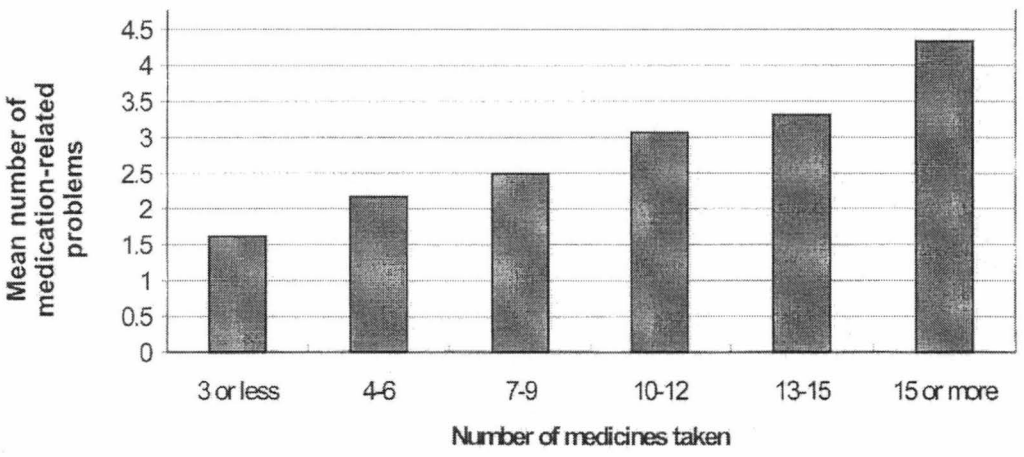
> "Data show that between two and three per cent of hospital admissions are related to problems with medicines (approximately 140,000 per year). This is more than the combined number of admissions for asthma and heart failure. Of the 100 million encounters recorded in general practice each year, it is estimated that around 400,000 of these are related to adverse medication events"[5].

Many studies in Australia and overseas have documented the prevalence of multiple drug use in elderly patients[57, 92, 93]. An average of from 2 to 6 prescribed

medications and 1 to 3 non-prescribed medications taken concurrently by elderly patients has been commonly reported in studies performed in a variety of settings[57].

Conventional wisdom has dictated that multiple drug use should be minimised, especially in elderly patients. General thinking has been along the lines that polypharmacy is unhealthy because it increases the risk of poor patient compliance, adverse drug reactions and drug interactions, particularly in the elderly, given the typical alterations in both the pharmacokinetics and pharmacodynamics of drugs with ageing, and impaired homeostatic mechanisms[94, 95]. Not surprisingly, as the number of medications are increased to a patient's regimen so too does the number of medication-related problems (Figure 4)[5].

Figure 4 Number of medication-related problems compared with medication use[5]



There is reasonably sound evidence that the use of multiple medications increases the risks of adverse drug reactions and drug interactions, and makes compliance with medication regimens more difficult[6, 12, 57, 96-102]. Drug-induced cognitive impairment in the elderly is particularly common with polypharmacy[103]. The number of medications that a patient is taking is one of the strongest predictors of drug-related

illness[100, 101]. Unnecessary medication has been estimated to account for 27% of drug-related hospital admissions[99]. It has also been estimated that 35% of ambulatory elderly patients with polypharmacy will report experiencing at least one adverse drug event within the previous year[102].

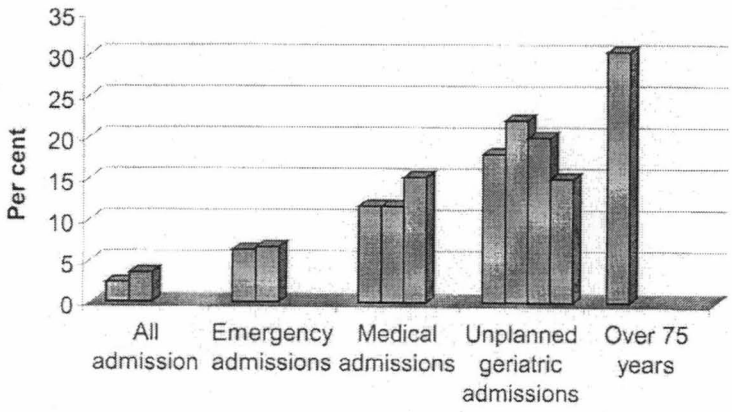
The causes of multiple drug use in elderly patients include: the increased number of diseases and chronic disorders experienced and the mistaken belief that all medical conditions in the elderly require drug therapy, people's desire to take medicines, the expectation of medication at each consultation, the attraction of novelty, habit, the pressures of drug promotion, and a failure to review medications regularly.[12, 18]

It had previously been estimated that problems associated with therapeutic drug use in Australia result in at least 80,000 hospital admissions annually (accounting for approximately 12% of all admissions to medical wards[4, 104-106] - including at the Royal Hobart Hospital[105]), at a cost of around $400 million per year[4, 104]. About one-half of these hospital admissions are considered to be avoidable. In a comprehensive review of international studies published between 1966 and 1999, Winterstein *et al*[107] recently concluded that preventable drug-related hospital admissions account for approximately 4% of hospital admissions. It is clear that adverse drug reactions remain a significant cause of hospital admissions[4, 104-106, 108] and unplanned readmissions[109-111], frequently involving predictable high-risk situations (e.g. multiple drug use in the elderly) which are amenable to prevention through improved health-care systems[112].

The well-publicised report by the United States (US) Institute of Medicine estimated that between 44,000 to 98,000 people die in American hospitals each year as the result of medical errors[113, 114]. About 7,000 hospital inpatients per year were estimated to die from medication errors alone - about 16% more deaths than the number attributable to work-related injuries. In Australia the situation is just as serious. As

previously stated, between 2-3% of all hospital admissions are medication related[5]. In older people (those over 65 years), approximately one in five unplanned admissions to hospital is medication related (Figure 5). This may be partly because older people are more likely to be taking one or more medications, and partly because they are more likely to be admitted to hospital and so be represented in hospital statistics[5].

Figure 5 Types of medication-related hospital admissions: Results from Australian studies 1988-2001[5]

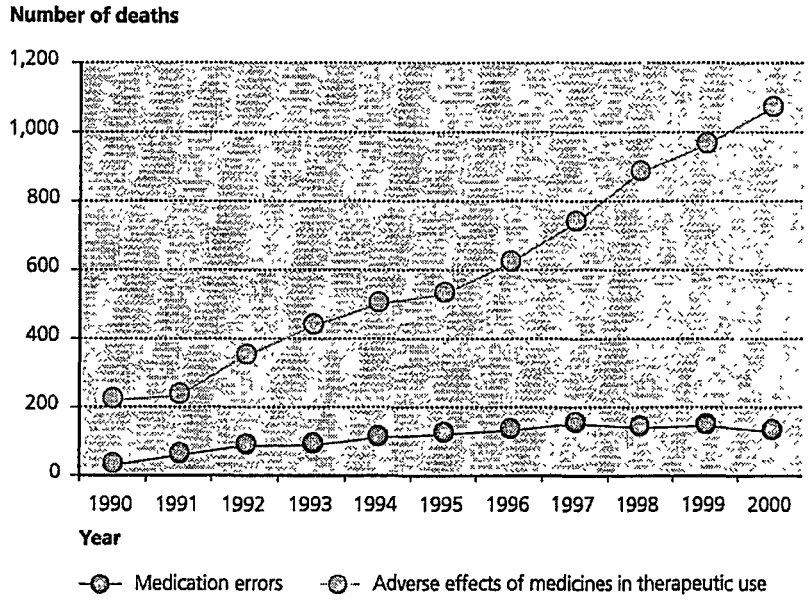


Adverse drug events, including medication errors, are the most common type of non-operative adverse event in hospitalised patients[90, 115, 116]. A meta-analysis of 39 studies from hospitals in the United States revealed an overall incidence of serious adverse drug reactions of 7% and of fatal adverse drug reactions of 0.3% in hospitalised patients[117]. It was estimated that in 1994 a total of 2.2 million hospitalised patients had serious adverse drug reactions and 106,000 had fatal adverse drug reactions, making these reactions between the fourth and sixth leading cause of death in the United States.

One of the most worrying aspects about adverse drug events, including medication errors in hospitalised patients is that they seem to be becoming more

common[118, 119]. There was significant media attention in the UK on the finding in the recent Audit Commission report on medicines management in hospitals that there had been a 500% increase in reports of medication-related deaths in England and Wales over the past 10 years (Figure 6)[118].

Figure 6 The number of deaths in England and Wales from medication errors and the adverse effects of medicines, 1990-2000[118]



An analysis of medication errors over a 9-year period found a progressively increasing risk of adverse drug events for hospitalised patients[119]. The most common types of errors were dosing errors and prescribing medications to which the patient was allergic. The increased rate of errors is possibly associated with increases in the intensity of medical care and use of drug therapy. New errors were encountered as new drug therapies were introduced. For instance, as more drugs are being released onto the market, the possibility of drug interactions tends to increase continually. A large

Swedish study concluded that 31% of elderly out-patients had at least one interacting drug combination, with the probability of a drug interaction increasing with multiple drug use[120]. Health care practitioners and health care systems must incorporate adequate medication-related error reduction, prevention, and detection mechanisms into the routine provision of care[112].

Factors contributing to medications incidents

Studies in hospitals have identified several common errors that contribute to medication incidents. Errors in administration of medicines, prescription ordering errors, dispensing errors, and lack of acknowledgement of previous adverse drug reaction and allergies are common reasons for medication incidents in hospitals. Similar errors occur in the community. Table 1 shows the types and rate of medication incidents and Table 2 shows factors contributing to these incidents in general practice.

Table 1 Types of medication incidents in medical practice[5]

Type of incident	Rate per 100 incidents
Drug inappropriate	30
Prescribing error	22
Administration error	18
Dose inappropriate	15
Side effect	13
Allergic reaction	11
Dispensing error	10
Overdose	8
System inadequacies	7
Drug omitted or withheld	6

Table 2 Factors contributing to incidents in general practice[5]

Contributing factor	Rate per 100 incidents
Poor communication between patient and health care professionals	23
Action of others (not GP or patient)	23
Error of judgement	22
Poor communication between health professionals	19
Patient consulted other medical officer	15
Failure to recognise signs and symptoms	15
Patient's history not adequately reviewed	13
Omission of checking procedure	10
GP tired/rushed/running late	10
Patient misunderstood their problem/treatment	10
Inadequate patient assessment	10

Some information on the types of dispensing errors is available from Pharmaceutical Defence Limited, the company (in Australia) that provides professional indemnity insurance for pharmacists. The most common types of errors are selection of incorrect strength of medication, incorrect product or incorrect interpretation of prescription[5]. For example, Prozac® (fluoxetine) being confused with Provera® (medroxyprogesterone)[5].

Having multiple health care providers may also cause problems with medications although there are no data on the extent to which this causes problems with consumers[5]. Similarly, patients hoarding medications may contribute to medication errors although no data are available on the extent that this leads to patient harm. In addition, patients may become confused with generic and trade names. One study found that consumers did not understand the difference between the trade and generic name of a medication[5]. Difficulty understanding medication labels can also lead to medication errors, although it is not known how often this occurs[5].

Poor communication at the time of discharge from hospital or errors in prescribing or transcribing at discharge can contribute to medication incidents[5].

Transition between hospital and the community

Discharge from hospital represents a period of high-risk for adverse drug events in elderly patients[121]. Significant alterations in a patient's medication regimen (drugs or dosages) may occur during hospitalisation and medications may not be taken appropriately after hospitalisation. Documented medication errors include continuation of medications that were discontinued at discharge, failure to start new medications, taking the incorrect dosage, and a lack of understanding of directions for medication use[121].

A review of discharge prescriptions for 68 patients at one Australian hospital found that 15% of the regular medications intended to be continued were omitted at discharge[122]. Similarly, Stowasser *et al*[123] reported that, on average, one medicine was omitted from the discharge prescription. There were also problems with the medication history on admission, with medications frequently not being documented.

It has been noted that the management of prescribed medications among chronically ill patients recently discharged from acute hospital care is often sub-optimal, and that an assessment of medication management in the home provides an invaluable opportunity to detect and address problems likely to result in poorer health outcomes[7]. For instance, patients may be confused after discharge despite comprehensive counselling by pharmacists or other hospital staff.

Stewart and Pearson studied 342 chronically ill patients discharged from acute care at the Queen Elizabeth Hospital, Adelaide[7]. At one-week post-discharge a home visit was performed by a nurse and a pharmacist, during which medication management (including compliance and medication-related knowledge) was assessed. During the majority of home visits, at least one medication-related problem was detected and

approximately half of the cohort was found to be poorly compliant. Other previously unknown problems detected during the home visit included hoarding of previously prescribed medication (35%) and reducing medication intake to minimise costs (21%).

Two South Australian studies by Stewart *et al* have also examined interventions to improve outcomes following hospitalisation[9, 124, 125]. The first study looked at the effect of a home-based intervention on readmission and death among a small sample of 'high-risk' patients with congestive heart failure discharged home from acute hospital care[9, 124]. Home-based intervention comprised a single home visit (by a nurse and pharmacist) at one week after discharge to optimise medication management, identify early clinical deterioration, and intensify medical follow-up and caregiver vigilance as needed. The home-based intervention was associated with reduced frequency of unplanned readmissions plus out-of-hospital deaths within 6 months of discharge from hospital.

The second study was directed at a range of medical and surgical patients[125]. Home-based intervention consisted of counselling of all patients before discharge followed by a single home visit (by a nurse and pharmacist) to those patients considered to be at high risk of readmission in order to optimise compliance with and knowledge of the treatment regimen, identify early clinical deterioration, and intensify follow-up of such patients where appropriate. Again, home-based intervention was beneficial in significantly limiting unplanned readmissions and reducing risk of out-of-hospital death. However, the effect of the intervention on the quality of medication use was not assessed directly in these studies.

Unplanned readmissions to hospital

Unplanned readmissions to hospital have a substantial impact on health care costs[109, 126, 127]. Approximately 5% to 29% of adults are readmitted within 30 days of a medical or surgical stay[128]. About 15% of older patients have an unplanned readmission[109]. Every tenth patient discharged from a medical department at a general hospital in Sweden during the period, 1992-1994, required emergency readmission within 14 days[129]. Another study reported a 30-day readmission rate of 21% following cardiac surgery[130].

A study conducted in Tasmania[131] involving over 500 medical patients (aged over 60 years and taking two or more regular drugs) discharged from the Royal Hobart Hospital found the unplanned admission rate within 6 months of initial discharge was 34%, and 8% of these readmissions were noted in the medical record as being drug-related.

Between 9% and 48% of all readmissions have been judged to be preventable because they were associated with indicators of substandard care during the index hospitalisation, such as poor resolution of the main problem, unstable therapy at discharge, and inadequate post-discharge care[127]. Many studies have attempted to identify precise factors that may lead to patient readmission. Problems with drug therapy have previously been identified as a major cause of readmission to hospital[109-111, 126, 132-136]. Several studies have reported that patients who had changes in their medication regimen before discharge were more likely to be readmitted within a month or less[137]. Studies of geriatric patients have found a drug-related readmission rate of up to 7% within six months of discharge[132, 133]. In an Australian study conducted at the Fremantle Hospital in 1991, the incidence of drug-related readmission of all adult patients was 1.9% within 60 days of discharge[134].

A retrospective case study analysis was conducted at the Monash Medical Centre, Melbourne[111]. Patient data stored by the medical information system were searched to identify patients readmitted within 60 days of discharge. This information was then linked with appropriate medical record ICD-9 discharge codes to identify patients re-admitted with drug-related diagnoses. Over one-third (35%) of the unplanned readmissions during the 4-month study period were documented as being caused by problems related to drug therapy. There was a significant trend of increased incidence of drug-related readmission in elderly and very young patients. The annual cost of drug-related unplanned readmissions to the hospital was estimated by extrapolation to be $650,000.

The majority of the drug-related problems identified in readmission studies are potentially preventable and the types of problems found have indicated that interventions should be focused on both hospital staff and patients[133, 136]. Randomised prospective trials have shown that 12% to 75% of all readmissions can be prevented by patient education, pre-discharge assessment, and domiciliary aftercare[127].

Poor compliance with therapy has frequently been identified as one cause of hospital readmission, resulting in 17 to 48% of all drug-related readmissions[132-134, 138]. It has been suggested that patient compliance with medication prescriptions after hospital discharge should be a major concern of all hospital staff, who need to play a role in determining whether discharge medications are used as ordered, whether complications which could lead to readmission are likely to result from poor compliance, and whether adequate measures have been instituted to maximise compliance[138].

Strategies to reduce medication incidents

Strategies that have been shown in published literature to reduce medication incidents are summarised in Box 1.

Box 1 Strategies that have been shown to reduce medication incidents[5]

- Use of computerised prescribing with clinical decision-support systems by doctors – information about medicines for health care providers on-line or in prescribing/dispensing software.
- Computerised adverse drug event alerts – these hold information about the patient's medical record and medication record, and automatically signal the presence or possibility of an adverse drug event when a medicine is prescribed.
- Individual patient medication supply in hospitals – medicines are labelled, supplied and stored for each individual patient, reducing the risk of wrong medication or wrong dose.
- Clinical pharmacy services – pharmacists in hospitals can support systems to reduce medication incidents, through patient and staff education, monitoring and medication review.
- Transfer of information between hospital and community settings – complete list of current medicines held by the patient and better transfer of information between hospital and community health professionals.
- Community based medication management services and case conferencing – assisting patients considered at high risk of medication-related problems through review of their prescribed, over-the-counter and complementary medicines, and discussion of their overall health care.
- Discharge medication management services – range of services for people at risk of medication incidents, including discharge and medication summaries to patients and health care providers.

Clinical pharmacy services within hospitals have been shown to reduce medication errors and system failures and are well established in Australia[5]. A survey undertaken in 1995 of Australian hospital pharmacy departments found that 87% were

involved in clinical activities to detect, correct and report medication errors. Ninety-six percent of departments provided medication chart review and 88% provided patient education and counselling[70].

Discharge liaison services are also an effective method for improving transfer of information and reducing medication-related problems when patients are discharged from hospital into the general community to their primary carers. The 1995 survey of pharmacy departments found only 18% of respondents offered a discharge liaison service[70]. There are little data on the effectiveness of liaison services post-discharge. Spurling *et al*[139] conducted a study to evaluate the effectiveness of a medication liaison service to reduce medication incidents for patients discharged from hospital. There was an intervention and a control group and the study found that the intervention group that received the liaison service (home visit within 48 hours of discharge) had fewer medication-related problems six weeks after discharge from hospital.

As discussed elsewhere in this thesis, Stowasser *et al*[140] found that patients whose GP and community pharmacist received medication liaison service post-discharge were less likely to be readmitted. In addition, another study found that patients who were visited by a nurse and pharmacist a week after discharge were less likely to be readmitted than a control group and also had a reduction in mortality[124, 125].

Aims of study

The aim of this research was to perform a randomised, controlled evaluation of a home-based follow-up of 'high-risk' patients following hospitalisation. The follow-up was by a clinical pharmacist, whose role was to ensure continuity of pharmaceutical care for patients and optimise the QUM. Specifically, we aimed to identify drug-related problems and attempt to resolve them and assess the impact on unplanned readmissions.

Chapter 2: Methods

Recruitment, exclusions and randomisation of patients

Patients were recruited from the Royal Hobart Hospital, a 400-bed acute care teaching hospital and the only major public hospital in the southern region of Tasmania. Patients admitted to the medical units at the hospital between November 2000 and December 2001 were eligible to participate if they were 60 years or older, had at least two chronic medical conditions requiring drug therapy (including at least one of heart failure, ischaemic heart disease, chronic obstructive airways disease or diabetes mellitus) and were prescribed four or more regular medications. Patients were excluded if they lived in a domiciliary care facility or beyond the greater Hobart area, were to be visited at home by a community health nurse within five days of discharge from hospital, had terminal malignancy or were unable to give consent.

Those patients who provided informed consent were allocated to either an intervention or control group by the pharmacist responsible for conducting the home-visits (MN), using a computer-generated list of random numbers. The pharmacist conducting the recruitment, randomisation and follow-up of patients was not employed within the study hospital, and the randomisation occurred the day after patients were discharged from hospital so that patients were blinded to their randomisation. An initial interview and review of medical records was conducted with all patients to document their baseline characteristics. Data recorded for each patient included demographic information, reason for admission to hospital, smoking habits, alcohol intake, medical history, medication history, and management during hospitalisation. All patients received regular medical, nursing and pharmacy care during their hospitalisation.

Home visit protocol

Medication review day 5

Patients were telephoned one day prior to the scheduled home visit to arrange a suitable time for the review. Five days following hospital discharge, patients in the intervention group received a single home visit by the study pharmacist. The objectives of this visit were to educate patients about their medications and answer any queries from patients or their caregivers, optimise medication management and improve compliance with drug therapy, detect otherwise hidden drug-related problems, and improve liaison with community-based health services. The control group received care from their usual health-care providers and did not receive a home visit until 90 days post-discharge.

Compliance assessment

The study pharmacist performed a pill count to assess the patient's compliance with their medication regimen. Prior to discharge, medications, dosages and quantities supplied were noted. It is the policy of the pharmacy department at the Royal Hobart Hospital to provide five days of medication to each patient at discharge. Patients were deemed non-compliant if they had taken more or less medication than prescribed. Patients who appeared non-compliant with medications (dispensed from the hospital) were questioned in a non-threatening way to determine if medication supplies the patient may have had at home prior to hospitalisation were being used as an alternative to the hospital supply. It was acknowledged beforehand that there are limitations to this method and its lack of scientific approach, however, no other method was available. Also during the visit, the patient was asked a modified compliance question:[141] 'People often have difficulty

taking their pills for one reason or another ... have you had any difficulty taking your pills?', 'About how often would you say you miss taking your pills?', with response options of 'once a day', 'more than once a week, but less than once a day', 'once a week', 'once a month', 'rarely', or 'never'.

Patients who were deemed non-compliant based on the pill count or who appeared to have poor understanding of their medications were offered a compliance device (e.g., Dosette box) or their community pharmacy was requested to provide additional services such as filling and delivering a compliance device (e.g. Webster pack). Where possible, family members were asked to provide increased support or community nursing was asked to provide services such as filling a compliance device.

Drug-related issues

The study pharmacist performed a comprehensive medication review to assess the need for all medications and identify any drug-related issues. The clinical pharmacy service complied with the Society of Hospital Pharmacists of Australia's standards of practice for clinical pharmacy[142]. Drug-related problems were pre-defined before the study utilising a modified categorisation by Cipolle *et al*[143]. *Drug Interactions Facts*[144] was used to categorise drug interactions. Only interactions reaching a significance of level 1 ('Potentially severe or life-threatening interaction; occurrence has been suspected, established or probable in well controlled studies') or 2 ('Interaction may cause deterioration in a patient's clinical status; occurrence suspected, established or probable in well controlled studies') were recorded as being potentially clinically relevant.

Software used in medication review

The following drug information software was utilised whenever necessary during the medication review:

- E-MIMS® 4.0 (MediMedia Australia Pty Limited, Vivendi Universal Health, St Leonards, NSW, Australia, May 2001).
- Electronic Therapeutic Guidelines® on disc - Analgesic 3rd edition 1997; Antibiotic 10th edition 1998; Cardiovascular 3rd edition 1999; Dermatology 1st edition 1999; Endocrinology 1st edition 1999; Gastrointestinal 1st edition 1998; Neurology 1st edition 1997; Psychotropic 3rd edition 1996; Respiratory 2nd edition 2000 (Therapeutic Guidelines Limited, North Melbourne, VIC, Australia).
- Drug Interactions Facts™ on disc (Facts and Comparisons, St Louis, MO, United States, November 2001).
- Clinical Pharmacology® 1.17 (Gold Standard Multimedia Inc, Tampa, FL, United States, 1998).

Transfer of information to patient's GP and community pharmacy

A brief letter, composed in the patient's home using a portable laptop computer and printer, was given to the patient to present to their doctor at their next visit (Appendix 3). The letter outlined the patient's medication regimen and any suggested changes or monitoring procedures. Immediately after the visit, the pharmacist telephoned the patient's GP and community pharmacy to inform them of the study and to discuss any urgent issues that arose from the visit. In addition, in more urgent cases, the letter was sent by facsimile to the GP.

Medication review day 90

There was no contact with patients in the control group (after the initial collection of baseline data which occurred during the patient's admission) until 90 days had elapsed. They (and the intervention group) were then visited at home and provided with a comprehensive medication review in an identical manner to the intervention group five days following discharge, including the subjective assessment of compliance. The patient's GP and community pharmacy were contacted to verify the patient's prescribed drug therapy.

Primary endpoints

The primary endpoints for this study were the number of unplanned readmissions within 90 days of initial discharge from hospital, total days of readmission and out-of-hospital deaths (ascertained, when necessary, by contacting relatives or the patient's GP and reviewing hospital records). Patient medical records were accessed to monitor for emergency department visits or hospital admissions. Patients were also asked during the 90-day visit if they had been admitted to any of the other private hospitals. Drug-related readmissions were assessed by reviewing documentation in the medical notes. Patients were only deemed to have a drug-related readmission if the medical team treating the patient documented it.

Other outcomes included the number of drug-related issues identified, number of prescribed medications, level of compliance with the drug regimen and number of patients taking non-steroidal anti-inflammatory drugs (NSAIDs), alone and in combination with either angiotensin-converting enzyme (ACE) or angiotensin II (AII) inhibitors.

The study pharmacist (MN) was responsible for the recruitment, randomisation, post-discharge visits to the intervention and control groups.

Satisfaction questionnaire

A multiple-choice 'satisfaction questionnaire', to be completed anonymously, was given to each intervention group patient after the 90-day follow-up, along with a reply-paid envelope (Appendix 5). The questionnaire had not been previously validated and was designed to only assess whether patients appeared accepting towards or against the intervention.

Cost benefit

The estimates for probabilities of readmission were based on the readmission rate reduction observed in the study. Nine common Diagnostic Related Group (DRG) codes were selected (Table 3) to assess an average cost of a medical admission. Cost for readmissions avoided were calculated by multiplying the average cost from the range of DRGs, by the number of re-admissions avoided per annum if such an intervention was implemented by the Royal Hobart Hospital where the intervention was conducted. The cost of the various DRGs was provided by a Clinical Coding Manager at the Royal Hobart Hospital who obtained them from the National Public Sector Cost Weights in the National Hospital Cost Data Collection (NHCDC). The average cost ($2850) for the selected DRGs (shown in Table 3) is very similar to the national average for all DRGs, which in 2000-2001 was $2933.

Total clinical pharmacist costs were based on employing a pharmacist full-time for one year. In addition, other costs taken into account included travelling time to visit

patients and overheads such as Dosette boxes and spacers. Costing for time taken to complete data collection forms, conduct other research, teaching or other clinical activities was not included in the analysis.

Table 3 DRGs utilised to estimate cost of a medical readmission

DRG	Brief DRG description	Average length of stay per DRG (days)	Average cost per DRG ($Aust)
B69C	TIA without complications	3.2	2281
E62C	Respiratory infection without complications	3.72	2581
E65B	Chronic obstructive airways disease without complications	5.16	3171
F63B	Venous thrombosis without complications	4.84	2687
F62A	Heart failure and shock without complications	5.66	3663
F70A	Major arrhythmia and cardiac arrest and complications	5.0	4789
F72B	Unstable angina without complications	3.15	2435
F74Z	Chest pain	1.78	1496
K60B	Diabetes without complications	3.39	2613
Average		**4.0**	**2857**

Storage of data and statistical analysis

Patient data were recoded electronically on a laptop computer and password protected. Patient data sheets were secured in a locked cabinet.

Statistical analyses were performed using Statview 5.01 (Abacus Concepts Inc., Berkeley, CA, United States). Data was evaluated for normality. Non-parametric techniques were principally used to describe patient characteristics and examine differences in variables between the groups of patients (MW U test) and within groups between study periods (Wilcoxon signed-rank test). Categorical data were analysed by chi-square or Fisher's exact tests; the latter was only used when at least one of the variables had less than five patients or events. Prior to the commencement of the study, it was estimated that 100 patients would be required in each of the control and intervention groups. This was based on the assumption that 25% of "high-risk" patients have unplanned readmissions within 90 days of initial discharge and this could be reduced to 10% (at 80% power). A p value less than 0.05 were considered statistically significant.

Ethics approval

The study was approved by the Royal Hobart Hospital Research Advisory Committee and the Southern Tasmania Health & Medical Human Research Ethics Committee. Project information was sent to the local Division of General Practice and local branch of the Royal Australian College of General Practitioners, prior to the commencement of the study.

Chapter 3: Results

A total of 402 patients initially met the study's inclusion criteria, of whom, 266 were excluded for various reasons (Table 4).

Table 4 Details of patient exclusion from study prior to randomisation

Reason for exclusion	n = 266
Refused to participate	12
Nursing home resident	87
Dementia	18
Terminal cancer	14
Seen by community nurse within 5 days of discharge	55
Living > 50 km from Royal Hobart Hospital	71
Required interpreter	9

There were only 12 eligible patients of the total cohort (8.2%) who refused to participate in the study. The predominant reason for refusal in 8 of the patients was that they could not perceive any direct benefit to them. Three patients refused because they were moving interstate. One patient refused because they were enrolled in another study and did not want to be involved in further studies.

There were 15 patients (8 intervention, 7 control) who had to be excluded from the study after randomisation (Figure 7). Two control patients were excluded because they died before they were discharged from hospital. One control patient was involved in a fatal car accident shortly after discharge and thus excluded. Two patients (1 control, 1 intervention) voluntarily withdrew from the study. Five patients (3 intervention, 2

control) were unable to be contacted at follow-up. Three patients (2 intervention, 1 control) who were discharged home were later admitted to a nursing home and hence excluded. Two intervention patients were excluded as they were discharged for intensive nursing follow-up and it was deemed inappropriate by the investigators to visit. The excluded patients were not included in the baseline analyses.

Figure 7 Patient recruitment, randomisation and follow-up

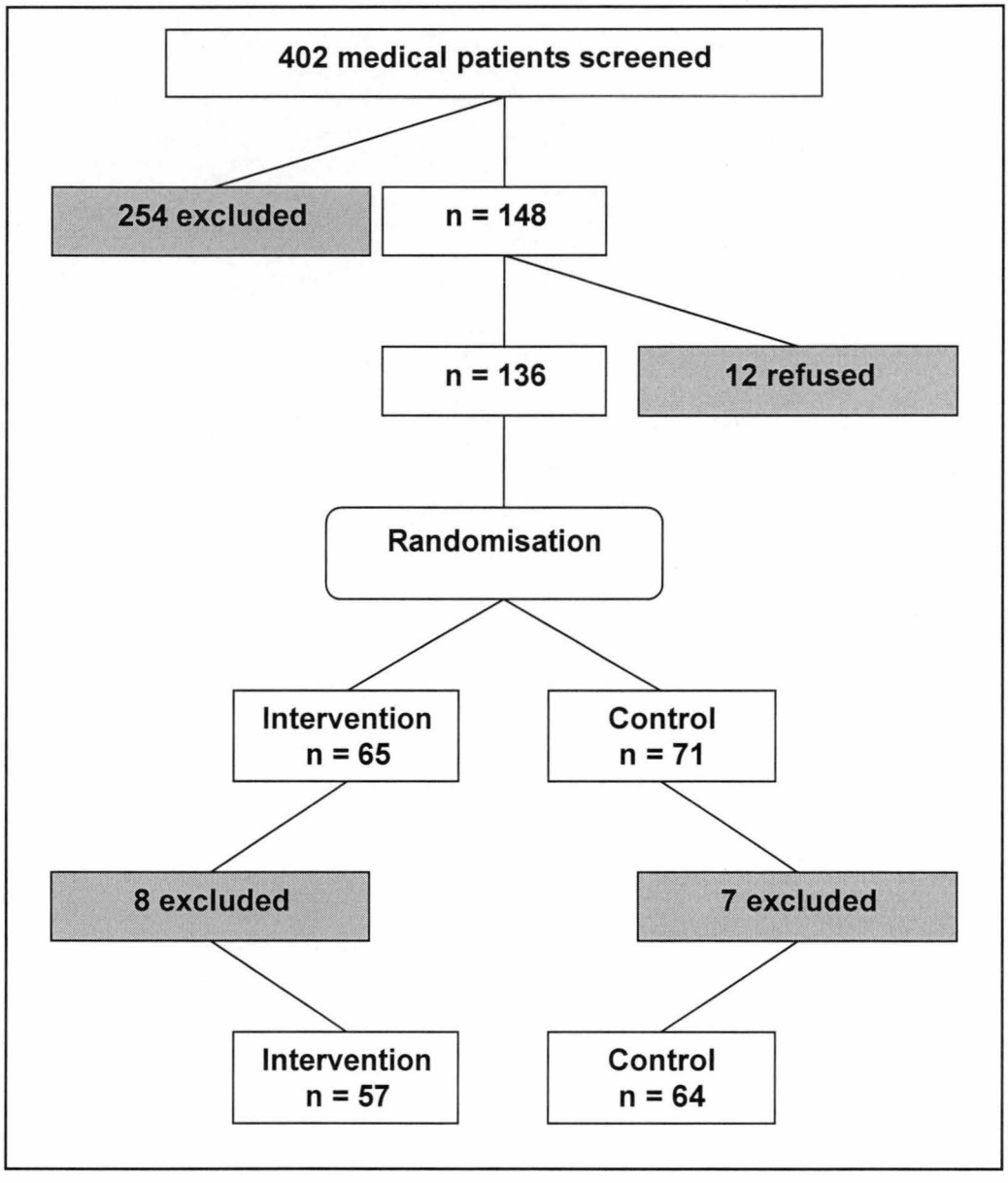


Table 5 summarises the clinical and demographic features of the 121 patients who completed the study. Analysis of the baseline data suggested that the two groups were reasonably well matched, with no statistically significant differences between the groups in any of the variables.

There were a total of 174 drug-related issues or problems identified in the intervention group (median 3 per patient) at 5 days post-discharge and this was reduced to 45 drug related issues at the 90-day follow-up visit (median 1 per patient). In comparison, there were 152 drug-related issues (median 2 per patient) identified in the control group at the 90-day follow-up (Table 6). Sixty-five percent of the intervention group patients, compared to 86% of the control group patients, had at least one drug-related problem at the 90-day follow-up ($\chi^2 = 7.3$, $df = 1$, $p < 0.01$).

The breakdown of the observed drug-related problems is summarised in Table 7. Clearly, compliance was a major problem in our cohort of patients, with 38% of the intervention patients found to be non-compliant, using a pill count, with one or more of their medications at 5 days post-discharge. Consequently, all of these patients received remedial counselling and were offered a compliance device/reminder routine. Whenever possible, closer supervision by a caregiver was arranged. Three patients were referred to community health nursing for home visit by a community nurse. The usual pharmacies of all non-compliant patients were notified for more intensive follow-up (if possible) after the visit.

Other significant problems or issues identified included the number of patients using their drug delivery system incorrectly, excessive or insufficient dosage of medications, incorrect timing for dosing of medication, taking discontinued medication, using medication that was perhaps not the safest or most efficacious, and not receiving a medication when indicated.

Table 5 Baseline characteristics of patients within the intervention and control groups

Patient characteristics	Control (n = 64)		Intervention (n = 57)	
Gender - male (%)	31		44	
Age; years (median & range)	77	(60 - 91)	74	(65 - 90)
Living alone (%)	45		47	
English as second language (%)	7		9	
Primary admission diagnosis (%) *cardiac disease* *respiratory disease* *gastrointestinal disease* *other*	 54 11 9 26		 56 14 4 26	
Nil or moderate alcohol intake (%)	91		92	
Smoker or ex-smoker (%)	63		67	
Seen by hospital pharmacist at discharge (%)	89		89	
Nursing assistance at home (%)	21		28	
Hospital stay, in days (median and range)	6	(1 - 94)	7	(2 - 42)
Unplanned admissions in previous 12 months (median and range)	0	(0 - 4)	0	(0 – 11)
Patients with an unplanned readmission within the previous 12 months (%)	42		47	
Chronic medical conditions (median and range)	5	(2 - 13)	5	(2 - 9)
Regular medications on admission (median and range)	6.5	(1 - 16)	7	(2 - 15)
Regular medications on discharge (median and range)	8	(3 - 16)	8	(3 - 15)

Table 6 Drug related issues identified within the intervention and control groups, with time

	Median drug-related issues identified per patient (range)	
	5 days	90 days
Control	Not Applicable	2[a] (0-8)
Intervention	3[b] (0-9)	1[a,b] (0-5)

[a] MW U = 634.5, z = -5.4, $p < 0.0001$ at 90 days
[b] Wilcoxon signed-rank test, z = -5.8, $p < 0.0001$ at 5 days versus 90 days

Examples of the "other" category of problems in Table 7 that were identified and attended to include:

- patients using medications that were out of date;
- patients not sure when to use certain medications (e.g., glyceryl trinitrate sublingual tablets/spray);
- patients using inhaled delivery devices when empty (e.g., Turbuhalers);
- the need to replace or service medication delivery systems (e.g., nebulisers, nebulising tubing or Dosette container);
- lack of community support and requiring increased services (e.g., community nursing); and
- diabetic patients not performing regular blood sugar levels when instructed.

There were 9 patients (16%) who were provided with a Dosette box or arranged to have a Webster pack filled and delivered to their home. Three patients (5%) were given a spacer to enhance compliance with medicated inhalers. Five patients were provided with accessories for their nebuliser, as it was deemed that these patients were not getting adequate delivery of the nebulised drug. Two patients had their nebuliser serviced. Four

patients (7%) were found to be not coping very well at home and had poor community support, and thus community health nursing was arranged to visit them and assist with medication. A list of examples (not exhaustive) of the interventions made by the study pharmacist is shown in the Appendix 4.

Table 7 Drug related issues identified during study

Drug-related issue	Intervention 5 days n = 57 (% patients)	Intervention 90 days n = 54 (% patients)	Control 90 days n = 59 (% patients)	Statistics[a]
Drug interaction[b]	45.6	42.6	50.0	$\chi^2 = 0.6$, $p = 0.43$
Non-compliance[c]	38.2	5.6	22.4	$\chi^2 = 6.5$, $p < 0.01$
Drug not given or taken when indicated	29.9	11.1	27.1	$\chi^2 = 4.6$, $p < 0.05$
Difficulty getting prescription	21.1	1.9	0	$p > 0.9$
Drug given or taken without indication	17.5	5.6	6.9	$p > 0.9$
Using drug delivery system incorrectly	17.5	1.9	25.9	$p < 0.001$
Excessive or insufficient dosage	15.8	5.6	27.6	$p < 0.01$
Incorrect time drug given	15.8	0	25.4	$p < 0.0001$
Drug used not safest or most efficacious	15.8	0	15.5	$p < 0.01$
Dispensing error	10.5	1.9	5.1	$p = 0.6$
Taking discontinued medications	10.5	0	5.1	$p = 0.24$
Drug allergy/adverse reaction	8.8	3.8	3.4	$p > 0.9$
Hoarding medications	7.0	0	0	
Patient not responding to therapy	5.3	0	5.1	$p = 0.24$
Unable to open medications	3.5	1.9	1.7	$p > 0.9$
Drug-food interaction	1.8	0	1.7	$p > 0.9$
Improper route of administration	1.8	0	0	
Therapeutic contraindication	1.8	0	5.2	$p = 0.24$
Duplicating medications	1.8	0	1.7	$p > 0.9$
Drug level monitoring required	0	1.9	8.6	$p = 0.21$
Other	31.6	1.9	20.7	$p < 0.01$

[a] p values are for differences observed between the control and intervention groups at 90 days. p value is Fisher's exact p value unless otherwise stated

[b] drug interactions of level 1 or 2 according to Drug Interactions Facts software (Facts and Comparisons, St Louis, MO, United States, November 2001)

[c] non-compliance measured as per pill count.

The interview and pill-count measures of compliance were compared in the intervention patients at the 5-day visit (Table 8). The sensitivity of the interview question (i.e. the subjective measure of compliance) was relatively high, and the overall accuracy on the interview method was approximately 67%. However, the positive predictive value was relatively low.

Table 8 Comparison of compliance using interview and pill-count measures

Interview	Number of patients (%)			
	Less than 100% of pills taken		100% of pills taken	
"Miss"	18	(55)	15	(45)
"Never miss"	3	(14)	19	(86)

$\chi^2 = 6.0$, df = 1, $p < 0.01$

Specificity 19/34 = 56%; sensitivity 18/21 = 86%; positive predictive value: 18/33 = 55%; negative predictive value: 19/22 = 86%; overall accuracy: 18/33 + 19/22 = 37/55 = 67%.

Table 9 shows that the intervention group had improved compliance at the 90-day follow-up and that there was a statistically significant difference between the intervention and control groups. When the intervention patents were asked how often they forgot to take their medications, 39% of patients answered that they "never" forgot their medications at the five-day follow-up visit. At 90 days this had increased to 87%. The control group reported that they "never" forget to take their medications in 42% of cases. The difference between the control and the intervention was statistically significant ($\chi^2 = 22.8$, df = 1, $p < 0.0001$). Compliance was not significantly related to the number of prescribed regular medications at either 5 or 90 days post-discharge.

Table 9 Differences between groups in observed and self-reported compliance

	5 days		90 days	
	Intervention (%)	Control (%)	Intervention (%)	Control (%)
Self report – (never miss medication)	39	N/A	87[a]	42[a]
Observed apparent compliance	61[b]	N/A	94[b,c]	78[c]

[a] $\chi^2 = 22.8$, df = 1, $p < 0.0001$
[b] $\chi^2 = 17.3$, df = 1, $p < 0.0001$
[c] $\chi^2 = 6.5$, df = 1, $p < 0.01$

The use of NSAIDs was relatively common in these elderly patients (Table 10). Furthermore, most of the patients taking a NSAID were also receiving an ACE or AII inhibitor; in fact more than 20% of all the patients were using this combination on admission to hospital (Table 11). Approximately half of the patients in the intervention and control groups had their NSAID ceased prior to discharge from hospital. It was quite alarming to note that the majority of patients in the intervention group that had had the NSAID stopped during their admission were taking it again when visited at 5 days. However, after consultation with the patient, their GP and community pharmacist, the majority of these patents were re-instructed to cease the NSAID - and this cessation was sustained, as only 9.3% of the patients were taking the combination at 90 days. The control group patients also appeared to frequently re-start their NSAID. There was a statistically significant difference between the control and intervention groups at 90 days with regards to the use of NSAIDs.

Table 10 Use of NSAIDs within the intervention and control groups, with time

	% Patients taking NSAID			
	Admission	**Discharge**	**5 days**	**90 days**
Intervention	26.3	8.8	24.6[a]	9.3[a,b]
Control	29.7	9.4	N/A	23.7[b]

[a] $\chi^2 = 4.6$, df = 1, $p < 0.05$
[b] $\chi^2 = 4.2$, df = 1, $p < 0.05$

Table 11 Use of ACE/AII inhibitors concomitantly with NSAIDs

	% Patients taking NSAID + ACE/AII inhibitor			
	Admission	Discharge	5 days	90 days
Intervention	22.8	7.0	21.1[a]	9.3[a,b]
Control	21.8	9.4	N/A	18.6[b]

[a] $\chi^2 = 3.0$, df = 1, $p = 0.08$
[b] $\chi^2 = 2.0$, df = 1, $p = 0.15$

The primary endpoint of the study was the occurrence of unplanned readmissions to hospital. There were a total of 67 (25 intervention, 42 control) unplanned readmissions during the 90 days post-discharge. Forty-five percent of patients in the control group were readmitted, compared to 28% of patients in the intervention group (Table 12). The length of time spent with the patient at 5 days was not related to the risk of unplanned readmission in the intervention group (MW U = 270.0, z = -0.91, p = 0.36). Other factors not associated with readmission in our cohort of patients were the length of time spent in hospital on the first admission (MW U = 1689.5, z = -0.1, p = 0.9) and the number of chronic medications at initial discharge from hospital (MW U = 1517.5, z = -1.0, p = 0.3).

Table 12 Summary of principal outcome measures

	Intervention 90 days (n = 54)	Control 90 days (n = 59)	Statistics[a]
Unplanned readmission (% patients)	28	45	$\chi^2 = 3.8$, $p = 0.05$
Total days in hospital during readmissions (median and range)	0 (0 - 30)	0 (0 - 50)	MW U = 1516.5, z = -1.9, p = 0.06
Death (% patients)	5	8	$\chi^2 = 0.3$, $p = 0.5$
Number of regular medications (median and range)	8 (3 - 16)	8 (3 - 17)	MW U = 1481, z = -0.3, p = 0.7
At least one drug-related issue (% patients)	65	86	$\chi^2 = 7.3$, $p < 0.01$
Drug-related issues identified per patient (median and range)	1 (0 - 5)	2 (0 - 8)	MW U= 634.5. z = -5.4, $p < 0.0001$
Self-reported compliance ("never miss medication"; % patients)	87	42	$\chi^2 = 22.8$, $p < 0.0001$
Taking NSAID (% patients)	9	24	$\chi^2 = 4.2$, $p < 0.05$
Taking NSAID + ACE/AII inhibitor (% patients)	9	19	$\chi^2 = 2.0$, $p = 0.15$

[a]All χ^2 tests, df = 1

Table 13 displays the reasons why the patients in the two groups were readmitted. There was a similar distribution of the admission types between the groups. Brief details of the 5 cases of drug-related readmissions are:

- severe bradycardia secondary to digoxin, atenolol and flecainide;
- unstable angina secondary to stopping atenolol;
- unstable angina plus exacerbation of heart failure secondary to poor compliance with all medication;
- hypoglycaemia secondary to decreasing oral food intake without altering insulin therapy; and
- amiodarone toxicity secondary to failing to reduce a loading dosage regimen after discharge from hospital.

Table 13 Reasons for unplanned readmission to hospital

	Intervention (number of patients)	Control (number of patients)
Drug-related	3	2
Related to, or an exacerbation of, existing condition	8	17
New condition (seemingly unrelated to previous reason for admission)	5	10

Drug interactions were relatively common in both groups of patients and their prevalence did not change over the course of the study (Table 7 and Table 14). However, almost none of the interactions warranted total avoidance of the combination of drugs; instead they could be overcome if there was monitoring of the patient and/or therapeutic drug monitoring. Examples of the drug interactions detected were:

- digoxin plus frusemide (level 1);
- warfarin plus amiodarone (level 1);
- simvastatin plus gemfibrozil (level 1);
- frusemide plus hydrochlorothiazide (level 2);
- atenolol plus diltiazem (level 2); and
- simvastatin plus diltiazem (level 2).

Table 14 Prevalence of drug interactions within the intervention and control groups, with time

Group and time	Drug interactions (level 1 or 2)		Drug interactions (level 1)	
	Number	% of patients	Number	% of patients
Intervention 5 days	42	45.6	19	24.6
Intervention 90 days	32	42.6	15	20.4
Control 90 days	48	50.0	20	24.1

Although a formal survey of the GPs involved with the intervention was not conducted, it is possible to assume from the oral feedback given that this sort of exercise was of benefit to their patients. The vast majority of GPs were positive and a number indicated that it was a useful and long overdue exercise. The acceptance of the suggestions made by the pharmacist following the 5-day visit of intervention patients was also high (79%). These are displayed in Table 15.

Table 15 Suggestions made and accepted by GPs

Drug-related problem	Suggestion made (n = 53)	Suggestion accepted and implemented (n = 42)
Dosage	18	14
Addition of drug	15	10
Removal of drug	13	12
Adverse reaction	5*	4
Blood test	1	1
Route	1	1

* e.g., monitor patient

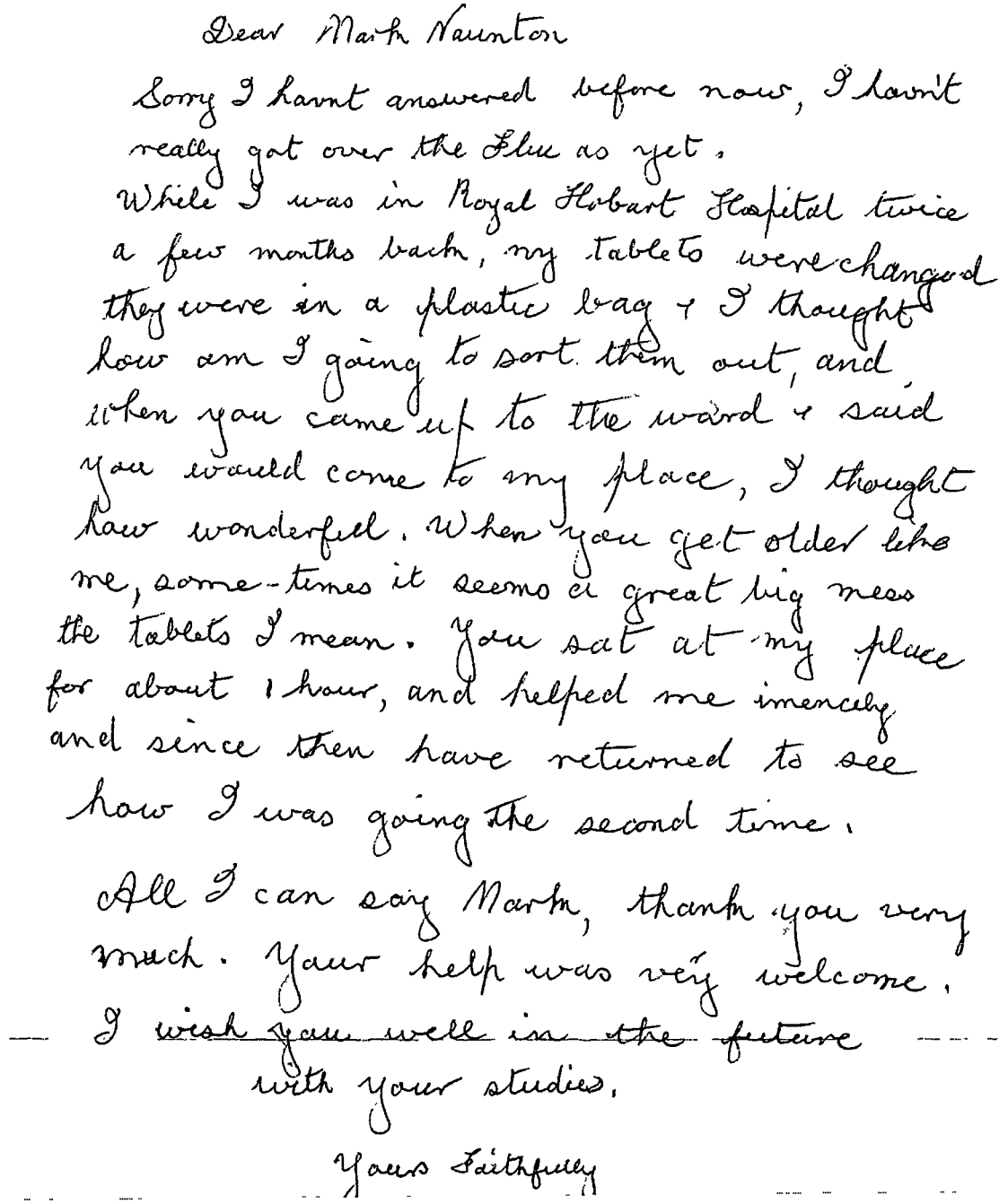
All patients were given the opportunity in the intervention group to contact the research pharmacist if they wanted to or felt the need to. There were a total of 15 calls from 10 patients. Often these calls were the result of a patient changing medication and he or she was seeking reassurance that the change would not adversely affect them.

The costs for undertaking this sort of intervention were minimal. The only direct cost involved was the time for the pharmacist to visit the patient and the on-road costs for travelling. Other costs included the provision of Dosette boxes to 9 (16%) patients and the supply of a spacer to 3 patients (5%). Also, 5 patients (9%) were given new nebulising accessories. The median duration of visit for the intervention group at 5 days was 50 minutes (range: 25 - 120 minutes). The median durations of the home visit for the intervention group and control group at 90 days were 30 minutes (range: 15 - 60 minutes) and 45 minutes (range: 20 - 90 minutes), respectively.

The intervention group patients were anonymously surveyed after the 90-day follow-up, and 32 completed survey forms were received from 51 patients given forms (63% response rate). Six patients in the intervention group were not given a survey to complete. Three patients died before the 90-day follow-up and therefore did not complete a survey. One patient was not given a survey because they were too unwell at the time of 90-day follow-up visit and it was deemed inappropriate to ask the patient to fill in and return the survey. Two patients were not given a survey because they could not read or write.

The responses are summarised below in Table 16, where the numbers represent the percentage of respondents selecting each item. Overall, there was an overwhelmingly positive response from the returned surveys, as shown in an example below (Figure 8) and in Appendix 6.

Figure 8 Patient survey response following home-visit.



Dear Marth Naunton

Sorry I havnt answered before now, I havn't really got over the Flue as yet.
While I was in Royal Hobart Hospital twice a few months back, my tablets were changed they were in a plastic bag & I thought how am I going to sort them out, and when you came up to the ward & said you would come to my place, I thought how wonderfull. When you get older like me, some-times it seems a great big mess the tablets I mean. You sat at my place for about 1 hour, and helped me imencely and since then have returned to see how I was going the second time.

All I can say Marth, thank you very much. Your help was very welcome.
I wish you well in the future with your studies.

Yours Faithfully

Table 16 Patient satisfaction survey

	%
How satisfied are you with the amount of contact you had with the pharmacist?	
Quite dissatisfied	6
Indifferent or mildly dissatisfied	0
Mostly satisfied	0
Very satisfied	94
Has the information and other services provided by the pharmacist helped you to deal more effectively with your medication?	
Yes, they helped a great deal	84
Yes, they helped somewhat	16
No, they really didn't help	0
No, they seemed to make things worse	0
Did you get the kind of information and other services you wanted from the pharmacist?	
No, definitely not	3
No, not really	3
Yes, generally	13
Yes, definitely	81
Is there other information you need, or would like, about your medication but have not received?	
Yes, there definitely is	0
Yes, I think there is	0
No, I don't think there is	59
No, there definitely is not	41
Overall, how would you rate the quality of the service that you received from the pharmacist?	
Excellent	94
Good	6
Fair	0
Poor	0

Cost benefit

The cost benefit of such an intervention if fully implemented at the Royal Hobart Hospital is shown in Table 17. In summary, for every dollar spent there is a saving of approximately $2, which translates to annual savings of approximately $158,000.

Table 17 Costs and total savings for implementing a post-discharge home-visit by a clinical pharmacist at the Royal Hobart Hospital per annum

		Cost per annum $Aust	
		Cost	**Savings**
Total number of patients who could have benefited from programme per year (met inclusion criteria for current study)[a]	1000		
Number of patients who would benefit given uptake of programme[b]	500		
Cost to employ one full-time pharmacist (including 20% on-costs)[c]		62,000	
Cost of expendables (mean $15 per patient)		7,500	
Cost of travel (including 20% on-road costs)[d]		15,000	
Total Costs		**84,500**	
Likely number of re-admissions prevented (17%)[e]	85		
Cost of readmissions prevented ($2850 per readmission)[f]			**242,250**
Total Savings			**157,750**

a. Assuming all medical patients screened during hospitalisation. Estimate based on a current project conducted at Royal Hobart Hospital.
b. Assuming half of patients excluded due to refusal to participate, dementia, requires interpreter, not discharged home, not receiving community health nursing and residing > 50 km from the hospital. Estimates based on a completed project and current study at the Royal Hobart Hospital.
c. Assuming 1 full-time (grade 2 level 1) pharmacist ($51,300 per annum) required to visit 10 patients per week post discharge.
d. Assuming 50 cents per km (average 30 km travelled per patient) and 20% depreciation on a $30,000 vehicle.
e. Estimate based on findings from current study.
f. See research methods.

Chapter 4: Discussion

The study examined medication management amongst a cohort of older, chronically ill patients recently discharged from hospital. It has demonstrated that there is clear evidence of problems relating to sub-optimal management of prescribed medications. Overall the medication control was relatively poor, with many previously undiscovered, and potentially serious problems unearthed during the home visit.

A major contributor to inadvertent polypharmacy and drug-related problems in the elderly appears to be hospitalisation and the consequent changes in medication (drugs or brands of drugs) at the transition from out-patient to in-patient care and back[6, 8, 9, 133, 145-148]. In a study of elderly patients receiving home health services, Gray *et al*[145] determined that self-reported adverse drug events were common during the month following hospital discharge.

The recently released Second National Report on Patient Safety of the Australian Council for Safety and Quality in Health Care ('Improving Medication Safety') concluded the following[5].

> *"Patients can leave hospital with a particular medicine, but may experience a breakdown in communication between their specialist and regular GP leading to inappropriate medicines being used. Patients and their carers may be confused by complex instructions, particularly when taking multiple drugs."*

Elsewhere in the report it was stated:

> *"It is essential for patient care that information about a patient's medicines is communicated to the hospital when the patient is admitted and back to their community health professionals when they are discharged. Poor communication at the time of discharge from hospital or errors in prescribing or transcribing at discharge can contribute to medication incidents."*

It is also well-documented in the literature that many patients have a poorly planned discharge and their GP is not fully informed of their patient's admission[149-155]. It was common for GPs to mention to the study pharmacist that there was poor communication from the hospital. In fact, 12 GPs (approximately 20% of intervention patients' GPs) made direct comments stating they were unhappy with the current discharge arrangements and appreciated the pharmacist contacting them to inform them of changes in their patient's drug regimen.

Recently, Wilson *et al*[151] found that GPs in the Macarthur Health Sector of New South Wales only received summaries from the hospital for 27% of 569 discharged patients. Of more concern was that 36% of discharge summaries contained information that did not reflect the information recorded in the hospital notes. These inaccuracies included medication (17%), clinical (17%), follow-up (14%) and clerical (2%) inconsistencies. Medication errors included incorrect medications recorded, medications omitted from the summary, and omission of dose or frequency. The same study showed that the recording rate of medications on discharge was 79%. This indicated that 21% of the summaries contained no indication of whether there were any variations in the existing medications or indeed any medications at all.

Wilson *et al*[151] suggested that perhaps junior medical officers may not be the ideal authors for writing the summaries due to their high turnover and that nursing and allied health professionals could contribute to the partial or total production of the summary, which may improve the quality and accuracy of the information. Stowasser *et al*[140] demonstrated that when a pharmacist communicated within 24 hours of discharge to patients' GPs, with a detailed summary of medication issues, there was a tendency for a reduction in readmissions within 30 days of discharge and there was a significant decrease in community healthcare professional visits (e.g. GP, domiciliary nurse, community pharmacist, medical specialist). The intervention's discharge communication contained information related to the following:

- list of medications on admission and discharge;
- corresponding therapy changes;
- intended duration of therapy, allergies and adverse drug reactions;
- new therapeutic devices; and
- medication-related problems and action required by the GP.

The study by Wilson *et al*[151] also suggested that the preferred method for delivering the discharge summary was via facsimile, combined with giving a copy to the patient, to ensure that if the patient visited a GP other than that nominated at admission, then appropriate information could be passed on. It was also stated that email is still not a preferred way of improving transmission of information, as many GPs still have not embraced this method of communication.

Mant *et al*[154] studied how hospital discharge information was communicated to GPs. General practitioners (n = 106) answered questionnaires about the type of

information they had received from the hospital about 203 of their patients. In only 22% of cases did the hospital directly notify the GP of the patient's admission. In 27% of cases the patient notified the GP, while in the remaining 52% of cases there was no notification given to the GP. A change to the patient's medicines was made in hospital in 87% of the cases, with the patient's medicine at discharge differing from what the GP understood the patient to be taking before they went to hospital in 72% of cases. Consultation with the GP about the patient's medication during the hospital stay occurred for only 11% of all patients. The mean time taken for GPs to receive the discharge summary from the hospital was 3 days, with a maximum of 21 days.

Under- and over-adherence to medications is common after hospital discharge[121, 138, 155]. Almost 39% of patients in the intervention group in this study had either taken more or omitted some of their medication within 5 days of their hospital discharge. The subjective assessment and objective measure of compliance were compared at 5 days. The sensitivity of the interview question was relatively high (86%). Previously published studies have indicated that patient interviews can provide a valid measure of compliance[141, 156, 157].

Interestingly, there were a high percentage (21%) of intervention group patients who had difficulty getting a prescription from a doctor or from a pharmacy when visited at 5 days. This is an important finding. It is possible that the patients who could have delayed obtaining the prescription were at risk of an early readmission because of non-compliance with their therapy. Conversely, over 10% of patients in the intervention group were found to be taking discontinued medications at 5 days post-discharge. This again highlights the valuable role of the pharmacist in identifying potential problems and intervening early before negative outcomes result.

There were a large number of potential drug-interactions (excluding ACE/AII inhibitors in combination with a NSAID) identified in both groups of patients. However, none of the interactions were deemed to require consultation with the prescriber, because they were not considered clinically relevant to the patient unless monitoring was not being performed. For example, it was not uncommon for patients with heart failure to be treated with an ACE inhibitor and spironolactone. The use of these two agents in combination can cause hyperkalaemia, especially in the renally compromised if adequate monitoring is not done. However, their use in combination is also advocated in the contemporary management of heart failure[158].

Often potential interactions were of a level 1 significance, however the combinations were not contraindicated (e.g., warfarin and amiodarone). Hence, while there were significant drug interactions, most did not require cessation of a drug, unless a patient had re-started a medication that had been ceased. For example, an elderly lady in the control group was found to be taking amitriptyline and cisapride concomitantly. The amitriptyline was initiated to assist with sleep by the patient's GP and the patient was experiencing some reflux and thus put herself back on cisapride (which had been stopped by the hospital) to treat her symptoms. It is well known that the combination of cisapride and a tricyclic anti-depressant greatly increases the risk of life-threatening cardiac arrhythmias, such as torsades de pointes[159].

One patient was found to be taking her atorvastatin 20 mg daily with a glass of grapefruit juice each morning, which may have resulted in the inhibition of metabolism, and possibly result in rhabdomyolysis[160, 161].

The combined use of a NSAID and ACE or AII inhibitor was chosen as an outcome measure of the QUM in this elderly cohort of patients. Both NSAIDs and ACE/AII inhibitors can lead to functional renal insufficiency[162-165]. In fact, NSAIDs and

ACE inhibitors are the main causes of drug-induced acute renal failure in the elderly[165] . This drug combination is commonly nephrotoxic in the elderly and should be avoided, especially in those taking diuretics[162-165]. It was of some concern to note that almost every patient in this study who was taking a NSAID was also taking an ACE/AII inhibitor. The intervention reduced the combined use of these potentially nephrotoxic agents, with the decline almost reaching statistical significance. We have also clearly shown that often patients re-commence medications that have been stopped during their hospital stay (e.g., NSAIDs), which can be remedied by a home visit from a pharmacist who has details of the patient's hospitalisation.

The results of this study, which demonstrate that a pharmacist following-up high-risk medical patients at home following discharge results in a reduction in drug-related problems and unplanned readmissions, lend support to the findings of overseas studies[166-169].

In a small, uncontrolled study with pre-post comparison, a pharmacist performing in-home medication evaluations on frail older people found that at the first visit, patients had a mean of 6.0 prescribed daily medications but were only taking 4.7 of these regularly[166]. Also noted were many potentially unnecessary medications (70% of patients) and multiple problems with the medication regimen (e.g. incorrect drug frequency or dosage, expired medications, medication omission). After patients were educated and recommendations were made to the prescribing physicians when necessary, a follow-up visit revealed a significant decrease in medication discrepancies and problems[166].

Lipton and Bird[167] assessed the impact of clinical pharmacists' consultations on drug regimens, compliance, and health service use of geriatric hospitalised patients (n = 706) discharged on 3 or more medications. Pharmacists consulted with experimental

patients at discharge and 3 months thereafter, and with physicians as needed. Controls received usual care. At 6-8 weeks after enrolment, experimental patients were more knowledgeable about regimens than controls. At 12-14 weeks, they were on fewer medications and less complex regimens, and had better compliance scores[167].

Schrecengost-Kibbey *et al*[168] recently reported on the outcome from the addition of a pharmacist to the team of providers offering home health services for older adults in Pittsburgh, Pennsylvania. The pharmacist visited patients newly enrolled in the programme at their homes or in a community centre. Medication appropriateness was determined for initial and follow-up visits. Taking a medical history and interviewing the patient identified drug-related problems and barriers to compliance. The pharmacist offered recommendations that could simplify therapy, improve medication compliance, or correct drug-related problems. A pre-post comparison showed that the pharmacist visits were effective in improving prescribing, and reducing drug-related problems and the barriers to compliance.

In a UK study, elderly patients discharged from hospital to their own home were randomised into control and study groups[169]. Control and study group patients received the normal discharge information. The study group were also counselled about their medicines and informed about their pharmaceutical care plan. Copies of the plan were given to the study patients. All patients received a domiciliary visit between 7 and 10 days after discharge. Their current medication was compared with that on discharge and contact was made with the GP as appropriate. Compliance was better ($p < 0.01$) in the study group. Unintentional changes to the medication of 31 (58%) patients were found during the visit and after contact with the prescriber all but one prescription was restored to that on discharge. It was concluded that a pharmaceutical domiciliary visit may be

useful to ensure seamless therapeutic care and thus avoid unnecessary healthcare events and costs after a patient is discharged home[169].

In contrast, Nazareth *et al*[170] reported no significant effect on the proportion of elderly patients readmitted to hospital between baseline and 3 months or 3 and 6 months with a co-ordinated hospital and community pharmacy discharge programme. Patients aged 75 years and older on four or more medicines who had been discharged from three acute general and one long-stay hospital were randomised to a pharmacy intervention or usual care. In the intervention group the hospital pharmacist developed discharge plans, which gave details of medication and support required by the patient. A copy was given to the patient and to all relevant professionals and carers. This was followed by a domiciliary assessment by a community pharmacist.

Rich *et al*[171] utilised a multidisciplinary strategy (comprehensive patient education, dietary and social service consultations, medication review by a geriatric cardiologist, and close follow-up after discharge) to improve medication compliance during the first 30 days following hospital discharge in elderly patients with congestive heart failure.

Wells *et al*[172] recently described a novel programme, designed to assist in teaching the principles of prescribing for elderly people, in which third-year medical students are involved a didactic session with a community pharmacist and a home visit to assess a senior citizen volunteer who was over age 75 years and was prescribed more than five medications.

An alternative approach to home visits is the follow-up of discharged patients by telephone. In a randomised controlled trial, Dudas *et al*[173] studied whether pharmacists can improve patient satisfaction and outcomes by providing telephone follow-up after hospital discharge. The intervention consisted of a follow-up phone call by a pharmacist

2 days after discharge. During the phone call, pharmacists asked patients about their medications, including whether they obtained and understood how to take them. A follow-up by phone call was associated with increased patient satisfaction, resolution of medication-related problems, and significantly fewer return visits to the emergency department.

There are some limitations to our study. Firstly, the same pharmacist assessed the drug-related problems in the control and intervention group at 90 days, introducing possible bias towards the intervention group at identifying possible drug-related problems. However, this was a secondary endpoint to the study and this would have no effect on the primary outcome measure of readmission to hospital. Secondly, our patient compliance question may have over-estimated actual compliance. We chose not to use a fully validated self-reported compliance questionnaire (e.g., Morisky scale[39]) as this was not a primary endpoint of the study and it was thought that focussing on each patient's compliance in-depth during the home visit may have been counter-productive to the overall intervention program. In addition, we may have under/over estimated compliance at the 5-day pill count because some patients may have been using (more or less) medications not obtained from the hospital. However, non-threatening questioning occurred throughout the visit to investigate if the patient was using medication not directly provided by the hospital. Thirdly, we may have under-estimated the true number of drug-related readmissions due to the retrospective assessment and by only including drug-related readmissions if they were clearly documented as such in medical records. Fourthly, our study consisted of a relatively small sample size that limited some of our interpretations and prevented us from determining exactly which patients may have benefited most from the home visit. Further research is required in larger

randomised controlled trials to assess the targeting and cost-effectiveness of such intervention programs.

This study illustrated that medication management is often not complex and relatively simple investigation and interventions by a pharmacist working closely and liaising with patients other care-givers can markedly improve the efficacy and safety of drug use in the elderly[174, 175]. While training and accreditation processes are important to ensure that pharmacists possess adequate clinical expertise when performing medication reviews, most drug-related problems in the community setting are not highly technical, and a perceived lack of clinical pharmacy knowledge should not act as a barrier to community pharmacists becoming more involved in patient-oriented activities[175]. What is more important is that someone showing an interest and taking time to ask the right questions and liaise with care-givers to sort out relatively simple problems that could have hazardous consequences if left unchecked. Pre-conceived ideas that doctors will not welcome advice or suggestions were not borne out in this study and it was the study pharmacist's experience that most GPs appreciated the interest of another professional in the care of their patient.

The results suggest that this sort of intervention merits a more widespread application in Australian hospitals. It was found using conservative estimates that if post-discharge care by a clinical pharmacist was implemented, the study hospital could save over $150, 000 per annum due to unplanned readmissions. This equates to a saving of approximately $2 for every $1 spent. A recently published study found that clinical pharmacy services within Australian hospitals was cost effective and there were savings from reducing length of stay in hospital and risk of readmission due to clinical intervention by hospital pharmacists[176].

More assistance needs to be given to patients, particularly those at 'high-risk' with multiple medications and several chronic medical conditions, when they are discharged from hospital. An in-home pharmacy assessment reveals many problems with drug administration not otherwise detected easily[166]. These assessments can lead to potentially useful interventions that can improve medication regimens and compliance. It may be particularly cost-effective if applied selectively to patients with a history of frequent unplanned hospital admission[166].

Discharge liaison services are an effective mechanism for improving transfer of information and reducing medication-related problems when patients move from hospitals back to the community[5]. However, it appears that this service is still under-developed in Australia. The 1995 survey of Australian hospital pharmacy departments found that only 18% of the responding departments were offering a discharge liaison service[70].

Chapter 5: Conclusion

This study has demonstrated the usefulness of a pharmacist in assisting with the management of medications. There was an improvement in patient compliance, fewer medication-related issues and a reduction in readmission. It was also shown patients and their GP welcomed the pharmacist-conducted follow-up post-discharge. Any therapeutic suggestions made to the GPs were largely implemented and the intervention appears to be cost-effective.

Part II: Pharmacist interventions to improve detection and treatment of osteoporosis

Chapter 1: Introduction

Osteoporosis poses a significant problem of epidemic proportions and is a major clinical issue associated with high morbidity and mortality in older women and men[177-182].

- Osteoporosis is largely preventable - essentially "the disease we *don't* have to have"[183]
- Already, nearly two million Australians have osteoporosis-related conditions - three quarters of whom are women[183].
- Osteoporosis is an expensive disease. It costs the country $1.9 billion per annum in health costs, with a heavy burden (68%) on hospitals and nursing homes. There are a further $5.6 billion in indirect costs. Osteoporosis is more expensive than either diabetes or asthma[183].
- Osteoporosis also cost Australians 25,000 years of healthy life in 2000-01, with over half of these years lost due to premature death [183].
- Osteoporotic fractures are expected to increase in frequency from one fracture every 8.1 minutes in 2001 to every 3.5 minutes in 2021 if nothing is done[183].

Almost any bone can fracture as a result of increased bone fragility from osteoporosis. It has been clearly shown that such fractures can profoundly threaten the quality of life of the elderly,[177, 180, 184, 185] and the consequences of ignoring osteoporosis or osteopaenia until fractures occur often are dramatic for elderly patients.

Pathophysiology of osteoporosis

Bone cells and the process of bone remodelling

During life, the skeleton undergoes remodelling, a periodic replacement of old bone by new, which is responsible for the complete regeneration of the adult skeleton every 10 years[187]. At the cellular level bone remodelling involves three cell types; osteocytes, osteoclasts, and osteoblasts, although bone is predominantly remodelled by a team of juxtaposed osteoclasts (front) and osteoblasts (back), comprising the basic metabolic unit (BMU)[187].

Osteocytes live in the lacunae inside the bone and are the most common cell type in bone. They communicate with each other and the surface of bone by way of channels that end in pores on the surface of the bone. Osteocytes detect microdamage to bone and signals to the surface of bone to control bone remodelling. They originate from osteoblasts (bone forming cells) that remain trapped in the bone after it is formed and mineralised[188, 189].

Osteoclasts are cells that act to dissolve and resorb bone and when activated, osteoclasts attach to the surface of bone. Osteoclasts then dissolve the mineral and protein of the bone by secreting hydrochloric acid and proteolytic enzymes beneath it. Osteoclasts may erode trabecular plates and rods and can resorb aggressively when oestrogen levels drop, for example, after menopause. If the rod or plate is thin enough,

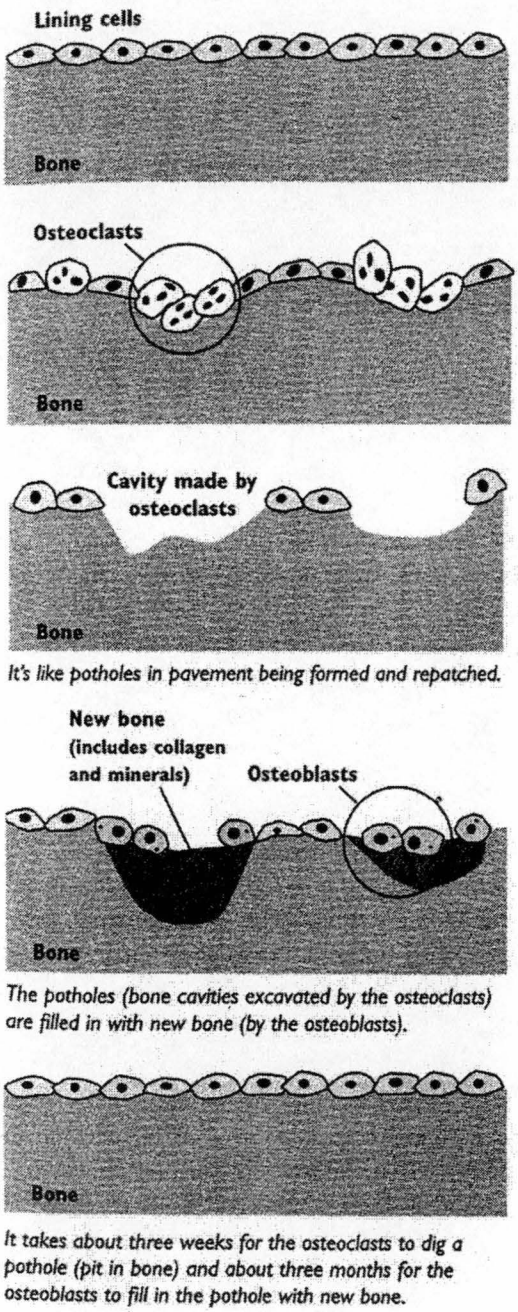
these aggressive osteoclasts may perforate or disconnect the structure and irreversibly weaken that section of the bone. Osteoclasts also work in groups to tunnel into cortical bone[188, 190].

Osteoblasts come from the same precursor cell line as fibroblasts and adipocytes and form bone by producing and secreting collagen and other proteins of the bone matrix that then assemble themselves. As soon as the osteoblasts lay down the protein skeleton, calcium and hydroxyapatite begin to crystallize around the collagen, and the bone begins to mineralise. As osteoblasts synthesise bone proteins, they also make a form of alkaline phosphatase, and some of the proteins they produce, such as osteocalcin, are released into blood where they can be measured to provide an indication of the rate of bone formation. Osteoblasts contain receptors for hormones, such as oestrogen, and are believed to generate the first signals that initiate bone remodelling[191].

In healthy human adults, 3-4 million BMUs are initiated per year and 1 million are operating at any moment[187]. Although bone is constantly remodelled, bone mass is preserved due to a remarkably tight balance between the amount of bone resorbed and formed during each cycle of remodelling. The BMU has an average lifespan of 6 months. The average life span of the osteoclasts is much shorter – 2 weeks, and the average life span of an osteoblast is 3 months. Evidence suggests that osteoclasts and osteoblasts undergo apoptosis once they have completed their bone forming tasks. Indeed, after osteoclasts have eroded bone to a particular distance, they die by apoptosis and are removed by phagocytosis. The majority of osteoblasts (50-70%) also die by apoptosis once they have completed their bone forming tasks. The remaining osteoblasts have one of two alternatives: they become elongated "lining cells" that cover the newly formed bone surface; or they can become entrapped in the mineralised matrix to become osteocytes[187].

In the normal process of bone remodelling, the activity of osteoclasts and osteoblasts are linked through chemical signals so that resorption of one microscopic section of bone is followed by formation of new bone in that spot (Figure 9).

Figure 9 Bone remodelling[192]



Mechanisms of bone loss

Bone loss can occur in several possible ways. Firstly, osteoclasts may create an excessively deep cavity, which cannot be filled by the action of the osteoblasts. Secondly, the function of the osteoblasts may be diminished, such that even a normal sized lacuna is not filled. Thirdly, an increased number of bone remodelling units can be activated which, when combined with either of the two above processes, may result in increased bone loss. For example, it is thought that the accelerated bone loss associated with menopause is related to an oestrogen-deficiency mediated increase in the number of active bone resorption units, as well as focal imbalance between osteoclasts and osteoblasts at each remodelling site[193].

Bone loss: cancellous vs. cortical bone

The overall architecture of bone is divided into cancellous bone (also referred to as trabecular bone), and cortical bone. Cortical bone forms a compact shell around the more delicate cancellous bone, which is formed by an interconnecting latticework of bone. In general the peripheral skeleton is primarily composed of cortical bone, while the axial skeleton is composed of both cancellous and cortical bone. Although cancellous bone may account for less than 25% for the total bone mass in healthy adults, its surface area far exceeds that of cortical bone. Additionally, cancellous is more metabolically active than cortical bone. Therefore, if bone remodelling becomes uncoupled, with osteoclastic activity exceeding osteoblastic activity, the mass and structural integrity of cancellous bone is more severely affected than cortical bone. During the accelerated period of bone loss occurring immediately post-menopause, cancellous bone loss is increased three-fold, while rates of cortical bone loss are slower.

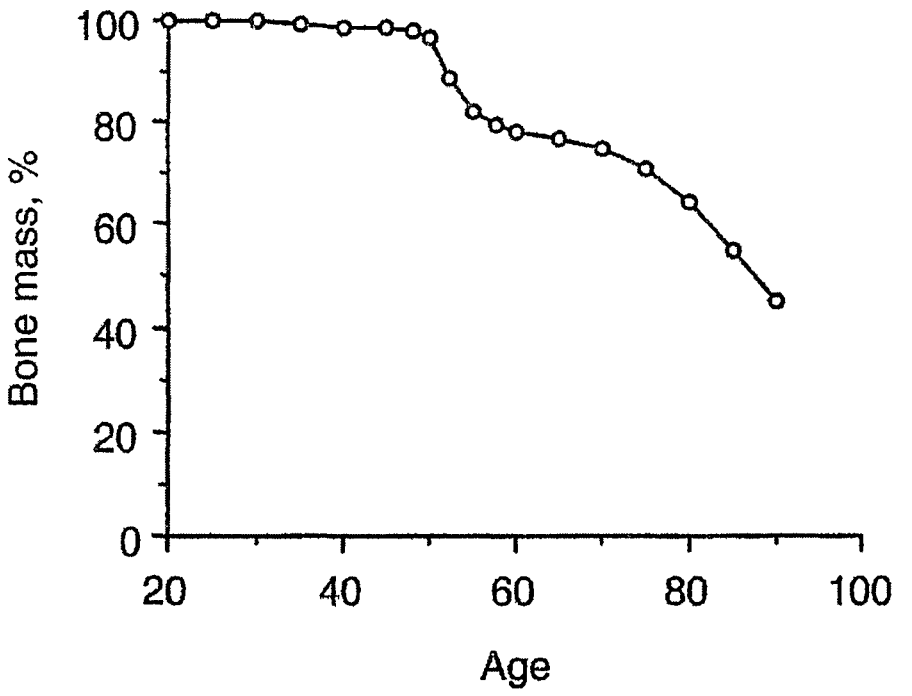
Therefore, fractures related to osteoporosis most commonly occur in areas rich in cancellous bone (i.e., the vertebrae and wrist), and BMD measurements have focused on these critical anatomic sites[193, 194].

Patterns of age-related bone loss

Bone mass increases progressively during growth, and may continue to rise for a period of time after adult height is achieved, representing consolidation of the skeleton. At skeletal maturity, men have 10-15% greater bone mass than women. Although the age of peak bone mass is uncertain, gradual bone loss begins in both men and women between age 30 and 40, paralleling an age-related decline in muscle mass. At the time of menopause, women begin a period of accelerated bone loss, averaging 2-5% per year over the next 10 years. This pattern of accelerated bone loss is seen only in women and is thought, though not proven, to be related to increased activity of the osteoclasts compared to the osteoblasts, and affects primarily the cancellous bone[195]. Accelerated bone loss is greatest in the first 3-6 years after menopause, levels off, and then gradually assumes the level of premenopausal bone loss[196]. When several years have elapsed since menopause, the rate of bone loss in the hip slows down then begins to accelerate again after age 70, reaching 1% or 2% per year in women older than 80 years[192] (Figure 10).

Men also gradually lose bone as they age, but because they do not undergo an acute menopause, there seems to be no accelerated period of bone loss. Exactly how much bone men lose during various decades has not been shown in longitudinal studies[192]. Testosterone levels gradually decline with advancing age, but low levels in elderly men have not been found to correlate with low bone density[197].

Figure 10 Percent of bone mass during a woman's adult life[192]



Definition of osteoporosis

The internationally agreed description of osteoporosis is 'a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures'[198]. The definition captures the idea that low BMD is an important component of the risk for fracture, but recognises that other abnormalities in the skeleton contribute to skeletal fragility[199]. There is a useful analogy with hypertension since blood pressure is used to diagnose hypertension, which in turn is a major risk factor for stroke[199]. Bone density accounts for most of the strength of bone tissue, and correlates with its load-bearing capacity. In fact, BMD can predict fracture risk, better than hypertension can predict the risk of stroke, or hypercholesterolemia can predict risk of myocardial infarction. However, bone mass, like blood pressure, represents a continuous variable, and there is substantial overlap in BMD values between patients with and without fragility fractures, suggesting a multifactorial aetiology of fractures. It is therefore arbitrary to define a specific cut-off point that distinguishes normal bone mass from osteoporosis[199].

Types of osteoporosis

Primary osteoporosis

Primary osteoporosis occurs independently of other diseases. In most patients, primary osteoporosis is classified as involutional osteoporosis, which has 2 subcategories: Type 1 (postmenopausal osteoporosis) and Type 2 (age-associated or senile osteoporosis)[200].

Type 1

Type 1 osteoporosis is a syndrome that typically affects women more than men (6:1), generally before the age of 65 years, because of its association with menopause. It affects 5% to 25% of women within 15 years of menopause, causing rapid bone loss (as much as 3-5% per year). In particular, trabecular bone loss is accelerated, resulting in vertebral crush fractures[200, 201]. The mechanism of postmenopausal osteoporosis is not completely understood but is most likely linked to oestrogen deficiency. However, although all postmenopausal women are relatively oestrogen deficient, only a small proportion of women develop Type 1 osteoporosis. Consequently, additional factors are likely to be involved, including diminished peak bone mass, increased bone resorption, impaired bone formation or a combination of these possibilities[200].

Type 2

Age-associated osteoporosis which involves both trabecular and cortical bone, occurs in older women and men; the ratio of female to male occurrence has been estimated at 2:1 to 3:1[200]. This disorder appears to affect older men who still have normal gonadal function and women who underwent menopause at least 15 to 20 years earlier[200]. Type 2 osteoporosis is characterised by less rapid bone loss (0.5% to 3% per year). The primary mechanism of bone loss is thought to be due to increased parathyroid hormone (PTH) secretion resulting from decreased gastrointestinal absorption of calcium and decreased osteoblast function[200].

Secondary osteoporosis

Secondary osteoporosis is defined as decreased bone mass attributable to an underlying aetiology[200]. There are a large number of clinical conditions and some medications that have been associated with osteoporosis in adults. The most common are shown in Table 18, although this is not an exhaustive list. Corticosteroid-induced osteoporosis is discussed elsewhere (Part IIb) in this thesis. Osteoporosis is also associated with depo-medroxyprogesterone used for contraception, although evidence on the effect on bone density is conflicting[202-204].

Table 18 Secondary causes of osteoporosis[205]

• Chronic renal disease	• Long-term immobilisation
• Rheumatoid arthritis	• Cushing's syndrome
• Male hypogonadism	• Primary hyperthyroidism
• Vitamin D deficiency	• Chronic liver disease (malabsorption syndrome)
• Anorexia nervosa	• Post-transplantation
• Inflammatory bowel disease	• Coeliac disease
• Long-term corticosteroids	• Long-term immobilisation

Assessment for osteoporosis

Bone mineral content

Measurement of BMD is the central component of any diagnosis that arises from the internationally agreed definition of osteoporosis. There are no satisfactory clinical means to assess bone quality. Diagnosis of osteoporosis therefore depends on the measurement of skeletal mass.

Single and dual X-ray absorptiometry (DEXA) are used to assess mineral content of the entire skeleton and that of specific sites[193, 205, 206]. Bone mineral content is the amount of mineral in the specific site scanned and, when divided by the area measured, can be used to derive BMD. DEXA is the most commonly used technique to measure BMD because of its ease, low radiation exposure, and its ability to measure BMD at the hip and spine (Figure 11)[205].

Figure 11 Example of a DEXA machine used to measure a patient's bone mineral density

Osteoporosis can often be diagnosed by looking at simple radiographs, albeit with low sensitivity[193, 205]. Quantitative tomography has been applied both to the appendicular skeleton and to the spine and is most useful in the assessment of cancellous bone density as it provides a true volumetric density, rather than area-adjusted as is the case with DEXA. The main disadvantages of computed tomography are high exposure to radiation, difficulties with quality control, and high cost when compared to DEXA[193, 205]. Skeletal status in osteoporosis can also be measured with quantitative ultrasound. The most widely used methods for assessing skeletal qualities are broadband ultrasound attenuation and speed of sound at the heel. Currently, ultrasound cannot be used for diagnosis of osteoporosis but there is solid evidence to support its use for assessment of fracture risk in elderly women[193, 205].

Of the many techniques that have been developed to assess bone mass, bone mineral content, or other related aspects of skeletal mass or structure, DEXA is regarded as the gold standard for diagnosis and monitoring of osteoporosis[205].

Biochemical assessment of bone remodelling

Biochemical indices of bone turnover can be divided into two groups: markers of resorption and markers of formation[207]. The principal markers of bone formation are total alkaline phosphatase, the bone isoenzyme alkaline phosphatase, osteocalcin, and the procollagen propeptides of type I collagen. The most widely used markers of bone resorption are hydroxyproline, and the pyridinium crosslinks and their associated peptides[205]. These can be measured either in urine or serum[208].

Bone markers can be used for several purposes including predicting future rate of bone loss, predicting risk of osteoporotic fractures, and monitoring response to

treatment[209], but they cannot be used to diagnose osteoporosis[208]. Bone markers are increased after menopause, and the results of several studies indicate that the rate of bone loss varies according to the marker value. It has been suggested that a combined approach, with BMD and indices of bone turnover, could improve fracture prediction in postmenopausal women[205].

Defining BMD diagnostic categories

Based on the increased risk of fracture with low bone mass, the report of the WHO Study Group divided patients into the following diagnostic categories based on BMD measurements (Table 19)[193].

Table 19 Diagnostic threshold for osteoporosis[193]

Normal	A value for BMD within 1 SD of the young adult reference mean (T-score ≥ -1).
Osteopaenia	A value for BMD greater than 1 SD above the young adult mean, but less than 2.5 SD below this value (T-score < -1 and > -2.5).
Osteoporosis	BMD 2.5 SD or more below the young adult mean (T-score ≤ -2.5).
Severe osteoporosis (established osteoporosis)	BMD 2.5 or more SD below the young adult mean in the presence of one or more fragility fractures.

The distribution of bone mineral content in young healthy adults (peak bone mass) is approximately Gaussian normal irrespective of the technique used. Because of the Gaussian distribution, bone density values in individuals can be expressed in relation to a reference population in SD units. When SD are used in relation to the young healthy population, this measurement is referred to as the T-score (Figure 12). Bone mineral density measurements may also be reported in terms of the Z score, which compares the BMD measurement to an age-and sex matched population. Z scores *are not* used to define osteoporosis, as they do not reflect the increasing prevalence of osteoporosis with age. For example, elderly patients may have a Z score of zero, based on comparison to their own group, but have a T-score that would put them in the osteoporotic category. Z scores are useful if they show that a patient's BMD is significantly below an age-matched group; this finding should prompt a more aggressive search for a secondary cause of osteoporosis[210]. With the use of an example, an explanation of the T and Z scores is shown in **Figure 13**.

Figure 12 Distribution of BMD in healthy women aged 30-40 years[205]

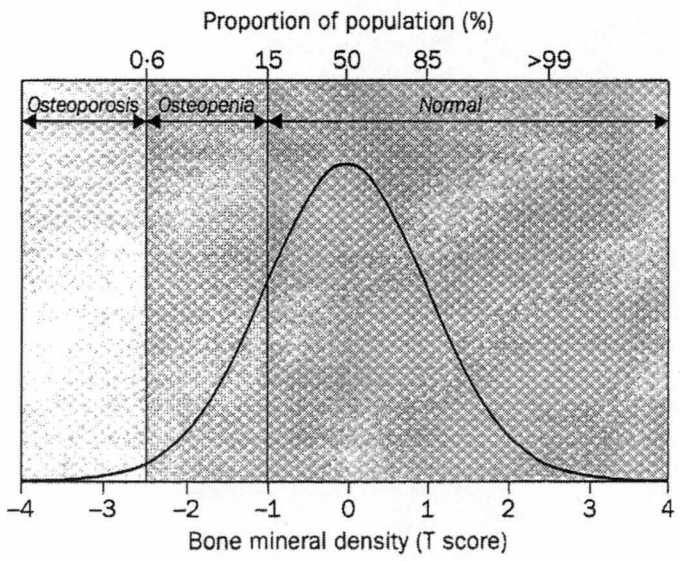
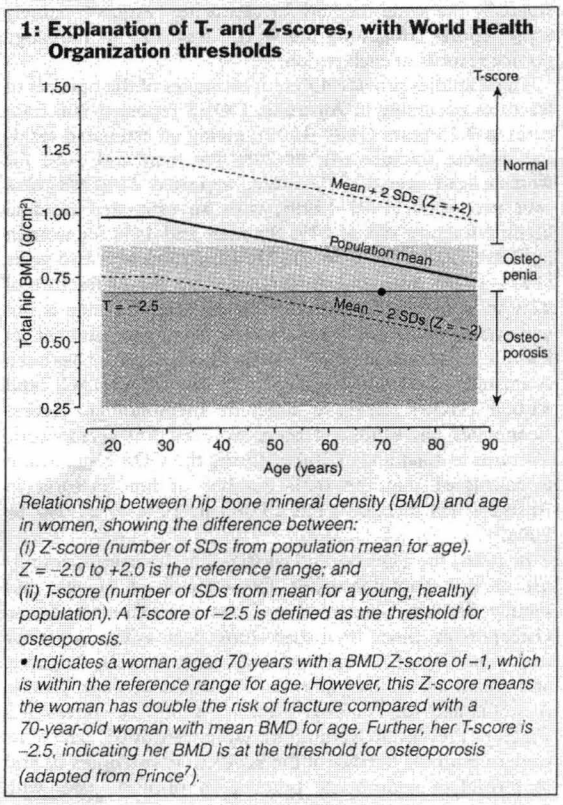


Figure 13 Explanation of the WHO T and Z scores[209]



Relationship between hip bone mineral density (BMD) and age in women, showing the difference between:
(i) Z-score (number of SDs from population mean for age). Z = –2.0 to +2.0 is the reference range; and
(ii) T-score (number of SDs from mean for a young, healthy population). A T-score of –2.5 is defined as the threshold for osteoporosis.
• Indicates a woman aged 70 years with a BMD Z-score of –1, which is within the reference range for age. However, this Z-score means the woman has double the risk of fracture compared with a 70-year-old woman with mean BMD for age. Further, her T-score is –2.5, indicating her BMD is at the threshold for osteoporosis (adapted from Prince[7]*).*

Limitations of diagnostic criteria

While the WHO diagnostic criteria for osteoporosis are based on T-scores, it should be noted there are several limitations to this approach in identifying patients with osteoporosis. These include: the use of different young normal reference databases with different instruments, other risk factors for osteoporosis beside BMD that are important, and the fact that BMD is only an intermediate outcome. Furthermore, suitable diagnostic cut-off values for men are less well defined than for women. The few studies available[211, 212] show that the risk of hip fracture is similar in men and women for any given BMD. Such studies indicate that a similar cut-off value for hip BMD that is used for women can also be used in men[205].

The choice of a reference range is important for the accurate classification of patients. In many countries reference ranges are not available for young healthy adults, and the use of manufacturers' ranges may be misleading. For example, published ranges that appear to be appropriate for the United States and northern Europe are not necessarily appropriate for other countries[213].

The T-score cannot be used for diagnosis interchangeably with different techniques or be based on measurements taken from different sites, since the same T-score derived from different sites and with different techniques yields different information on fracture risk. The intersite correlations, though usually significant, are inadequate for prediction, giving rise to errors of misclassification because of biological variations in BMD, and because of technical errors of accuracy[205].

Measurment of BMD at the hip remains the gold-standard for the diagnosis and monitoring of osteoporosis in terms of site, since it has the highest predictive value for hip fracture, which is the most severe complication of osteoporosis and predicts risk of all fractures as well as other techniques[214]. Measurements with DEXA at other sites should therefore be used for risk assessment and not diagnosis.

Epidemiology and consequences of osteoporosis

Based on the WHO definition, it is estimated that 30% of all white postmenopausal women in the United States will be diagnosed with osteoporosis (Table 20), and 54% will have low bone mass at the hip, spine, or wrist. More than half the women with osteoporosis will have a history of prior fracture of the proximal femur, spine, distal forearm, proximal humerus or pelvis[193].

Table 20 Proportion (%) of women with osteoporosis in United States (1990)[215]

Age group (years)	Lumbar spine (%)	Either hip site (%)	Midradius (%)	Spine, hip or midradius (%)
50-59	7.6	3.9	3.7	14.8
60-69	11.8	8.0	11.8	21.6
70-79	25.0	24.5	23.1	38.5
≥ 80	32.0	47.5	50.0	70.0
Total	16.5	16.2	17.4	30.3

Osteoporosis fractures represent an enormous public health burden. Worldwide, there was an estimated 1.66 million hip fractures in 1990, about 1.2 million occurring in women and 0.5 million in men[216]. Osteoporosis is a serious concern because it predisposes to fractures that cause pain, disability, occasionally premature death (Figure 14) and ultimately an increased economic cost to society[217]. The epidemiology of fractures is complicated because each fracture type has its own pattern that varies with factors such as age, gender, and even regions of the world[215]. Adults who sustain a fracture are more likely to sustain further fractures of a different type[218]. The most

common and severe types of fractures are hip fractures, vertebral fractures, and wrist fractures[193], with hip and vertebral fractures having been the most extensively studied[182]. Fracture incidence in the community is bimodal, with peaks in youth and advanced age)[178] and occurs in both urban and rural populations[219] (Figure 15).

Figure 14 Cumulative survival probability by sex and type of fracture[182]

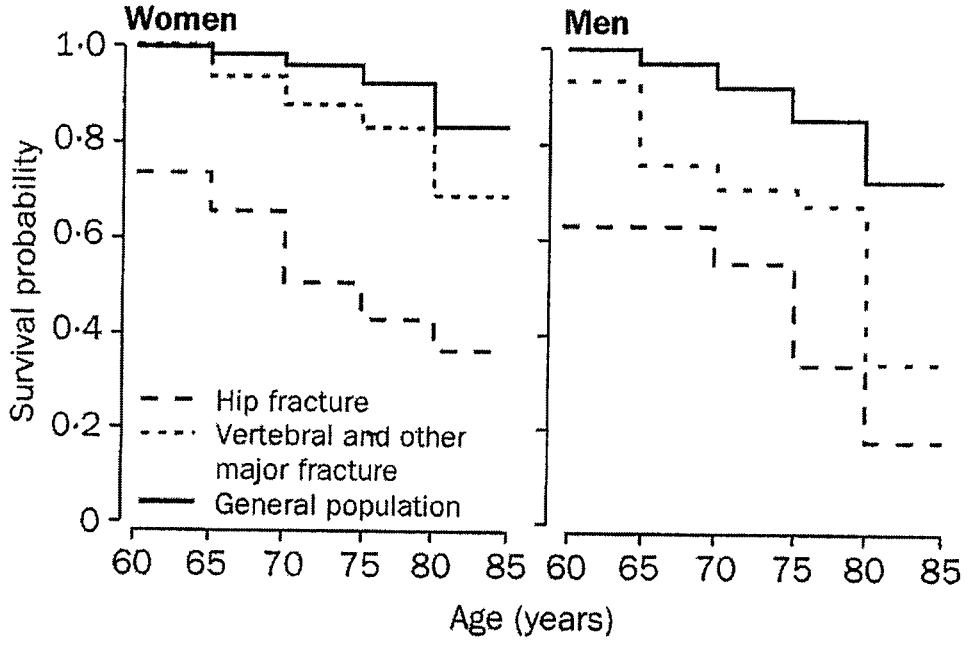
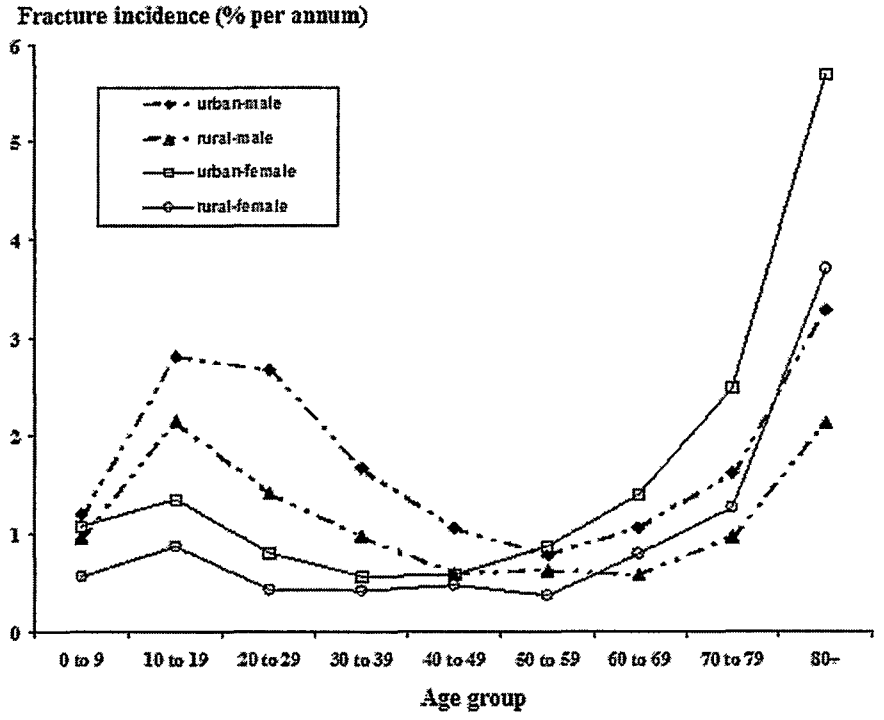


Figure 15 Lifetime fracture incidence for males and females in urban and rural areas[219]



Hip fractures

Life expectancy is reduced by hip fracture. Twenty percent more patients die within the first year after a hip fracture than would otherwise be expected for age, commonly due to co-morbidities such as deep vein thrombosis and pulmonary embolism resulting from immobilisation associated with the fracture[186]. For many previously fit patients, it means loss of full mobility and for others an inability to continue to live at home. At 1 year after a hip fracture, approximately 40% of patients are unable to walk independently, 60% are limited in at least one class 1 activity of daily living (e.g. feeding, dressing, toileting), and 80% are limited in a class 2 activity of daily living (e.g. shopping, gardening, climbing stairs). Furthermore, about 27% of hip fracture patients will require

nursing home placements; after 1 year this figure falls to 14%, although 30% will still need home care support[220].

Hip fractures account for more than 75% of the costs, much of the disability, and the majority of deaths due to osteoporosis[184]. Hip fractures are strongly correlated to low BMD, cost more to repair and cause more disability than any other osteoporotic fracture[182]. It has been demonstrated that hip fractures increase exponentially with age in men and women in most regions of the world[182]. Women have more bone loss and falls than men and thus their incidence of hip fractures is twice that seen in men in the United States, Europe[182] and Australia[221]. Furthermore, women live longer than men such that 80% of all fractures occur in women[178]. The lifetime risk of hip fracture from age 50 years onward has been estimated at 17% for white women compared with only 6% for white men[222].There is also marked geographical and ethnic variation in the incidence of hip fracture worldwide (for further discussion - see risk factors ethnicity) Lower hip fractures have been reported in rural populations compared to their urban counterparts[219, 223].

About 90% of hip fractures in both sexes result from a simple fall from standing height or less[224]. The risk of falling is high, increasing from 1 in 5 women aged 45-49 years to nearly half in women aged 85 years or older, along with a third of elderly men per year[224].

Hip fractures are likely to increase more than fractures at other sites because the greatest population growth is expected in the oldest age groups, where the hip is the most common site of fracture[225]. Furthermore, in contrast to Europe and North America, where numbers of hip fractures are expected to double by 2026 and then stabilise, in Australia hip fractures will continue to place a growing demand on healthcare resources for many decades. A fourfold increase in hip fractures is expected by 2051, when about

23% of Australia's projected population will be aged 65 years and over (compared with 12% in 1996), and 8% of the population will be aged 85 years and over (compared with 2% in 1996)[225].

In contrast to reports of an increase in fracture incidence, some recent studies have shown a trend-break in hip fracture incidence[226-228]. For example, Swedish researchers recently found that although there is likely to be an increase in trochanteric fractures (36%), there will be a 11% total reduction in all hip fractures for men and women[226].

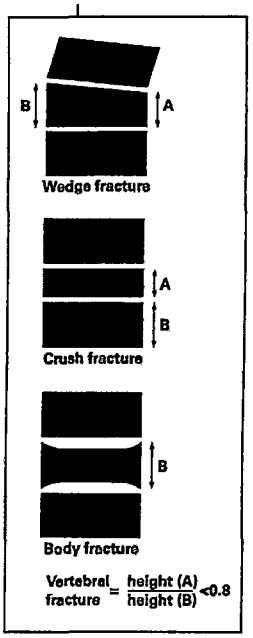
Vertebral fractures

Compared with hip fracture, the epidemiology of vertebral fracture is less well characterised. This is predominantly due to the lack of universally accepted diagnostic criteria of what defines an osteoporotic vertebral fracture. In addition, substantial proportions of vertebral fractures are asymptomatic and therefore escape clinical detection. It has been noted that the prevalence of vertebral fractures can vary up to three-fold depending on the criteria used to define vertebral fracture[229]. A lateral X-ray of the spine will often show a previously unrecognised fracture. A commonly used definition for diagnosing vertebral fractures is illustrated in Figure 16 and can be described as a crush, wedge or body fracture[230].

Patients with spinal osteoporosis suffer from vertebral deformation, loss of height and back pain, as well as from functional limitations and alterations of mood from anxiety and depression to social withdrawal and isolation[231]. Many fractures appear to arise without pain. However, women with vertebral deformities, incidentally found in routine radiographs of populations, are more likely to complain of chronic back pain, as well as suffer future fractures[182]. When a vertebral fracture causes acute symptoms, the

pain typically resolves over weeks or months[232], although there is a more protracted clinical course in a proportion of patients[233].

Figure 16 Diagrammatical definition of vertebral fractures[230]



Approximately one-third of all vertebral deformities noted on radiographs come to medical attention, and less than 10% come to necessitate admission to hospital[234]. Furthermore, even if there is a vertebral fracture on the radiograph, it is often not mentioned by the radiologist or noted in the medical records of the patient and therefore often treatment is not commenced[235]. This was recently demonstrated in a study of older (over 60 years) white women in the United States that found that fewer than 2% of the women received diagnoses of osteoporosis or vertebral fracture, although the expected prevalence is 20% to 30%. Indeed, appropriate drug treatment, including antiresorptive agents and calcium and vitamin D, was offered to only 36% of the diagnosed patients[236].

The incidence of vertebral fractures increases with age in both sexes. Most studies indicate that the prevalence of vertebral fractures in men is similar to, or even greater than, that seen in women to age 50-60 years. After about 60 years of age, women

in the United States and Europe have about a 2-3-fold greater incidence of vertebral fractures than men[234, 237].

A history of vertebral fracture, even an asymptomatic fracture, increases the likelihood of further vertebral fracture at least fourfold. This is independent of bone density so that vertebral fractures that arise with minimum trauma signal an underlying bone fragility that is not measured by bone densitometry. Fractures such as this are regarded as clinical evidence for the diagnosis of osteoporosis[237] . Vertebral fractures, like hip fractures, are associated with a similar increase in mortality at five years[238]. This increase is gradual over the five years, unlike hip fracture which is highest within the first 6-12 months following fracture[239]. More recently, a 10-year follow-up of Swedish patients with vertebral fractures demonstrated a prevalent vertebral deformity could predict both increased mortality and increased fracture incidence during the following decade in both men and women. The authors concluded that prevalent vertebral deformity could be used as a risk factor in both genders for mortality and future fracture[240].

In contrast to hip fractures, vertebral fractures result from falls in only 25% of cases[234]; most are precipitated by routine activities – bending or lifting light objects that can produce remarkably large loads, capable of causing vertebral fractures[241].

In a population-based study, an increase in most types of fractures occurred following a clinically recognised vertebral fracture among 820 persons in the United States. During 4349 person-years of follow-up there was a 2.8-fold increase in the risk of any fracture, which was greater in men than women. The data show that vertebral fractures represent an important risk factor for fractures in general, not just those of the spine and hip[242]. Another study by Black *et al*[243] demonstrated that women (and

probably men) who have a vertebral fracture also have a 2-fold increased risk of other fractures, such as hip fractures.

Efforts to identify other risk factors has been described as inconsistent[244]. Age, prior fracture, established osteoporosis, decreased height, and physical activity have been associated with vertebral fractures in men and women in a European study[245]. Other risk factors that have been reported for women include late menarche, early menopause, short duration of fertility, low calcium intake, low level of exercise, and family history of hip fracture. Ever use of the oral contraceptive pill has been associated with a 25% reduction in risk of deformity, though the effect may be a result of the higher-dosage oestrogen pills used in the past. Parity and breast-feeding do not appear to be important and would appear to have little potential for identification of women at high risk of vertebral deformity[246]. The consumption of alcohol also appears to have a protective effect for reducing risk of vertebral fracture[247]. Current moderate exercise has been associated with a reduced risk of vertebral deformity in women. By contrast, heavy levels of physical activity in early and middle adult life are associated with an increased risk in men[248].

Other fractures

Fractures other than hip and vertebrae have also been associated with low bone density[249, 250]. These include the proximal humerus, pelvis, proximal tibia as well as distal femur and increase with age in elderly women and to a lesser extent in men[182]. Most fractures have their own unique pattern of occurrence with age[249]. For example, wrist fractures are the most common fracture in perimenopausal women and rapidly rise after menopause, probably due to age related factors[182, 215]. Most wrist fractures occur outside, and a winter peak in incidence has been associated with icy weather[251].

Risk factors for osteoporosis and fractures

Several factors contribute to the development of osteoporosis-related fractures and these are shown in Table 21. It is beyond the scope of this thesis to describe each in detail and therefore some common risks are briefly discussed.

Table 21 Risk factors for osteoporosis[252]

Major risk factors	Minor risk factors
• Age > 65 years	• Rheumatoid arthritis
• Vertebral compression fracture	• Past history of clinical hyperthyroidism
• Fragility fracture after age 40	• Chronic anticonvulsant therapy
• Family history of osteoporotic fracture (especially maternal hip fracture)	• Low dietary calcium intake
• Systemic corticosteroid therapy of > 3 months duration	• Smoker
• Malabsorption syndrome	• Excessive alcohol intake
• Primary hyperthyroidism	• Excessive caffeine intake
• Propensity to fall	• Weight < 57kg
• Osteopaenia apparent on x-ray film	• Weight loss > 10% of weight at age 25
• Hypogonadism	• Chronic heparin therapy
• Early menopause (before age 45)	

Low BMD

Bone mineral density is the best predictor for developing an osteoporotic fracture. While BMD cannot be used to predict fracture certainty in a given individual, it does reflect fracture risk. The relationship between bone mass and future fracture risk has been documented in several prospective studies[253-256]. Estimates of relative risk are typically

based on the number of SD the BMD falls below the mean for young healthy adults with a decrease of 1 SD being associated with at least a 2-fold increase in fracture risk[214]. Figure 17 illustrates the exponential relationship between bone mass and fracture risk. In this figure, it can be noted that the exponential rise in fracture incidence starts at about –1 SD of bone mass; this fracture relationship is best established in those over the age of 65 years[257]. Figure 18 demonstrates the risk of hip fracture is very high when osteoporosis is present, but the risk of fracture is by no means negligible when BMD is normal[205].

Figure 17 BMD at various sites and incidence of vertebral fractures[257]

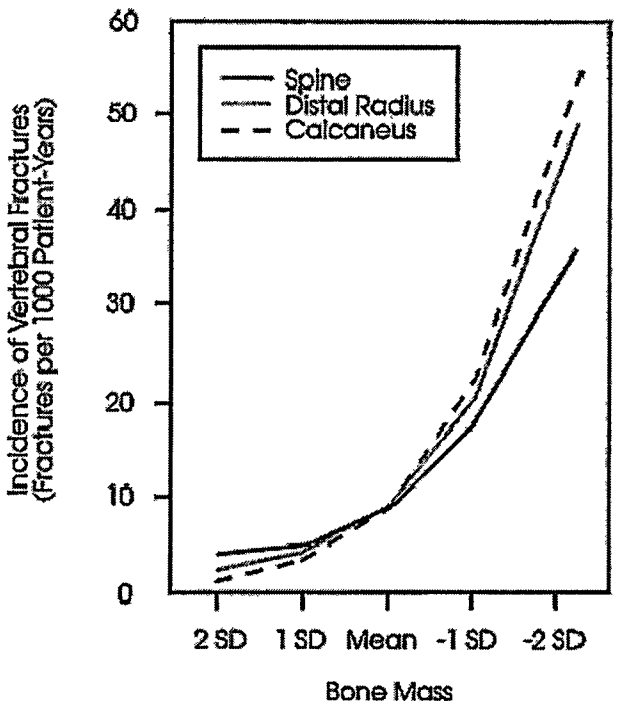
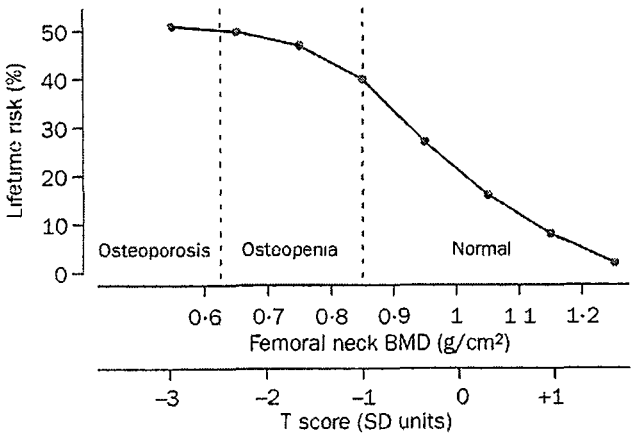


Figure 18 Remaining lifetime risk of hip fracture in women aged 50 years, according to BMD or T-score at the hip[205]



Falls

Because fractures are frequently associated with falls, a history of falls or factors that increase the risk of falling should be included in the assessment of risk. Risk factors for falling include those associated with general frailty, such as reduced muscle strength, impaired balance and low body mass[252]. Reduced visual acuity also increases the risk for falls[252]. It should be noted that falls cause fractures irrespective of whether a patient has osteoporosis, but a person who has osteoporosis is at even greater risk if he or she has a propensity to fall[252]. A prospective study[258] of elderly ambulatory women identified three factors that were significantly predictive of risk for subsequent hip fracture and were independent of hip BMD: a slower gait, difficulty performing a heel-to-toe walk and reduced visual acuity.

The pathophysiology of falls is complex. Risk factors for falls are shown in Table 22[259].

A meta-analysis of fall prevention trials found that there was a significant (10%) risk reduction in falls associated with exercise such as flexibility, balance, lower extremity resistance training and multidisciplinary physical therapy[260]. The exercise does not need to be strenuous as demonstrated by a Tai-Chi training programme that resulted in a 40% reduction in risk of falls[261].

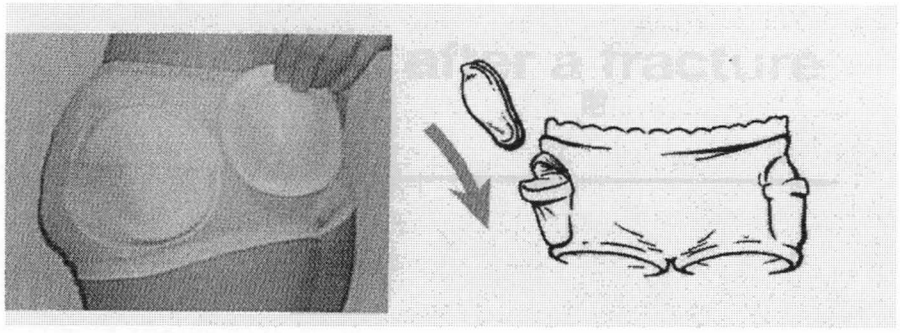
Table 22 Risk factors for falls[259]

Demographic factors
• Older age (especially ≥ 75 years)
• White race
• Living alone
• House bound
Historical factors
• Use of cane or walker
• Previous falls
• Acute illness
• Chronic conditions, especially neuromuscular disorders
• Medications, especially the use of 4 or more prescription drugs
Physical deficits
• Cognitive impairment
• Reduced vision
• Difficulty rising from chair
• Foot problems
• Neurologic changes
• Decreased hearing
• Others
• Environmental hazards
• Risky behaviours

A meta-analysis published from the Cochrane Collaboration indicated that interventions which are targeted at both intrinsic and environmental risk factors of individual patients reduces risk of falls, although less is known about their effectiveness in preventing fall-related injuries[262]. This indicates that fracture risk (in particular hip) also depends on the biomechanics of falling[182]. There is no evidence for the effectiveness of hip protectors (Figure 19) from studies in which randomisation was by individual patient within an institution, or for those living in their own homes[263]. Birks and colleagues[264] randomised 366 men and women aged 70 years and over who had sustained one hip fracture and who were living in the community, to receive hip protectors. They concluded that there was no benefit of the studied hip protector among people living outside residential accommodation. However, hip protectors may help reduce risk of fractures in nursing home residents who are at high risk of falling[263, 265], although not all studies have found these aids to be effective[266].

Multidisciplinary programmes that include a variety of techniques such as education, environmental modification, exercise programmes, medication management, and provision of free hip protectors may reduce falls and fractures among patients in residential care facilities[267]. There appears to be sufficient clinical and economic evidence to support the use of hip protectors for institutional dwelling elderly[268, 269].

Figure 19 Example of how a hip protector is worn[270]



History of previous fracture

Women who have suffered a previous fragility fracture (defined as a fracture occurring after a fall from a standing height or less) are at increased risk for further fractures, independent of BMD[271]. The increased risk is 1.5 to 9.5-fold depending on age at assessment, number of prior fractures and the site of the incident fracture[252].

Vertebral fractures have been the best studied in regard to future fracture. Women who develop a vertebral fracture have a 20% risk of a further vertebral fracture within one year[272]. In non-black women, the presence of one or two vertebral fractures increases the risk of further fracture by over 7-fold[273]. Men and women aged over 65 years with a vertebral fracture have a five-year risk of sustaining a femur or hip fracture of 6.7% and 13.3% respectively[218]. Those people at highest risk of fracture are those who have already fractured, including those with a loss of height or kyphosis (often painless) which can indicate the presence of vertebral fractures[274, 275]. Similarly, wrist fractures predict vertebral and hip fractures. Patients with a hip fracture are at increased risk of a second hip fracture. Pooling results from all studies (men and women) and for all fracture sites, the risk of subsequent fracture among those with a prior fracture at any site is 2-3 times that of people without a prior fragility fracture[252].

Age

Age is clearly a major contributor to fracture risk. As summarised by Kanis *et al*[276] in a recent review, the 10-year probability of experiencing a fracture of the forearm, humerus, spine or hip increases as much as 8-fold between the ages of 45 and 85 for women and 5-fold for men (Table 23).

Table 23 Average 10-year probability (%) of an osteoporotic fracture by sex, age and BMD expressed as T-score[252]

Age (years)	Overall average probability	T-score				
		1	0	-1	-2	< -2.5
Men						
50	3.3	1.8	2.7	4.2	6.3	9.2
55	3.9	1.9	3.0	4.6	7.0	10.4
60	4.9	2.5	3.6	5.4	7.9	11.6
65	5.9	3.0	4.3	6.2	8.8	13.0
70	7.6	3.4	5.1	7.4	10.9	16.2
75	10.4	4.1	6.3	9.6	14.4	21.5
80	13.1	5.3	7.7	11.1	15.8	23.2
85	13.1	5.3	7.5	10.4	14.3	21.4
Women						
50	6.0	2.4	3.8	5.9	9.2	13.9
55	7.8	2.6	4.1	6.7	10.7	16.8
60	10.6	3.2	5.1	8.2	13.0	20.5
65	14.3	4.0	6.3	10.0	15.6	24.9
70	18.9	4.3	7.1	11.5	18.3	29.8
75	22.9	4.2	7.0	11.8	19.4	32.6
80	26.5	4.6	7.7	12.7	20.5	34.4
85	27.0	4.5	7.4	12.0	19.1	33.1

Bone mineral density decreases, and consequently the risk of osteoporosis increases with age[252]. The Tasmanian Older Adult Cohort (TASOAC) study of approximately 229 600 men and women of all ages reported 2140 fractures over 2 years (1997-1999), with an estimated residual lifetime fracture risk of 27% for men and 44% for women aged over 50[221]. The Dubbo Osteoporosis Epidemiology Study of a cohort of about 3700 Australian men (1600) and women (2100) aged over 60 years reported 306 fractures in 3.25 years (1989-1992), providing an estimated residual lifetime risk of 29% for men and 56% for women aged over 60[277]. The United States National Health and Nutrition Survey (NHANES) III survey of postmenopausal women showed that the prevalence of osteoporosis in non-Hispanic white American women was 27% (50-59 years), 32% (60-69 years) and 41% for those aged over 70 years[278]. A previous estimate

based on data from Rochester, Minnesota indicated a lower prevalence of 14.8% (50-59 years), 21.6% (60-69 years), 38.5% (70-79 years) and 70% for women greater than 80 years (Table 20)[215].

Sex

Women are at greater risk of osteoporosis as they have smaller bones, live longer and have more bone loss and falls than men. It is therefore not surprising that they have a higher incidence (2-fold) of hip fracture than men[182]. Osteoporosis is less common in men although it remains a significant problem[279]. Secondary causes of osteoporosis are, however, more common in men, affecting approximately 40-50% of cases[280]. There are important exceptions. For example, in China where the overall risk of fracture in low, men and women have similar rates of hip and non-spinal fractures. In fact, males have slightly higher risks, although the reasons for this are not understood[281]. There are several populations, including the Maoris in New Zealand[282] and the Bantus in South Africa[283] in which the incidence of fracture in men is equal to, or greater than that seen in women.

Reproductive factors

Bone mineral density declines most rapidly immediately after menopause[284]. There is also consistent evidence to suggest that women who have an early menopause (< 45 years) have lower BMD[285]. There is inconsistent evidence that supports lower BMD in women who breastfeed, sustain miscarriages, have had tubal ligation, or association with parity status. In fact, larger studies has consistently shown that women who have had more children and breast-fed more babies have no increased risk, and perhaps even have

a slightly lower risk of fractures than other women[286]. Current use of HRT is associated with an increase in BMD, and a meta-analysis by Torgerson *et al*[287] demonstrated a statistically significant lower risk of nonvertebral fractures in women who used HRT. Pasco *et al*[288] analysed data from the Geelong Osteoporosis Study[289] and found that HRT reduced the risk of sustaining a fracture and increased BMD. The Women's Health Initiative (WHI) demonstrated that women who used combined HRT sustained fewer fractures than those using placebo[290, 291].

Family history

There is significant variation in the maximum bone mass achieved early in life and most of this is hereditary[292, 293]. It is most likely that many genes are involved in the determination of bone loss and these are yet to be elucidated. A family history of fractures indicates an increased risk of fractures[205], however this seems generally specific to the type of fracture. For example, a family history of wrist fracture indicates an increased risk of wrist fracture, and a family history of hip fracture indicates an increased risk of hip fractures independent of BMD at the hip[294]. Researchers in one epidemiological study found that the greatest risk for osteopaenia was in those whose fathers had a history of osteoporosis[295].

Ethnicity

It has been well established that white women have a higher incidence (2.5-fold greater risk) of osteoporosis than non-white women[278]. Asian women also have an increased risk for osteoporotic fracture[296] and the risk of fracture can vary from region to region. Hip fractures are most common in northern Europe, North America, and Hong Kong[215] Age-

adjusted incidence rates are higher among white women in Scandinavia than in women of comparable age in North America[182]. Women in Latin America or China have risks of hip fractures that are less than one third of the rates observed among white women in the United States. Rates of fractures in southern Europe are substantially lower than those in northern Europe[297]. Rates of hip fracture are higher in urban than in rural areas of the same country[219, 223, 298], and this suggests factors relating to urbanisation are responsible for the increased risk of fracture such as decreased physical activity and conversion from softer ground to hardwood, tile, concrete and asphalt surfaces[182].

Weight

Low body mass index is an indicator for low BMD and those in the lowest tertile suffer a doubling of bone loss compared to those women in the highest tertile and are considered at higher risk of osteoporosis[284].

Smoking

A meta-analysis of studies investigating the effect of smoking found that BMD in smokers was 2% lower with each increasing decade after menopause than in non-smokers[299]. Cornuz and colleagues demonstrated that women smokers have a greater risk of hip fracture than non-smokers, with increasing risk with increasing consumption. The level of risk declines upon cessation of smoking, but not significantly until 10 years after ceasing[300].

Alcohol

Contrary to popular belief from patients, moderate alcohol (1 to 3 standard drinks per day) is associated with a higher BMD and a lower risk for fracture in men and women[247, 301]. Alcoholism, however, has been associated with an increased risk for osteoporosis[302] and long-term heavy alcohol consumption may increase the risk of hip fracture[303]. It is thought that the beneficial effect of moderate alcohol consumption is possibly related to the augmentation of endogenous oestrogen levels by alcohol[304]. However there is some inconsistency of the benefit of moderate alcohol consumption on BMD[305].

Exercise

Observational studies demonstrate a positive relationship between physical activity and BMD. Conversely, immobility or a decrease in physical activity results in a decrease in BMD and higher rates of hip fractures[306]. Studies have shown that trained athletes have a higher BMD than non-athletic controls[307], and others have shown that higher BMD is associated with current exercise in postmenopausal English women[308] and in Norwegian women aged 50-75 years[309]. However, an Australian study found that the relationship between physical activity and BMD did not remain statistically significant after adjustment for age, BMI, calcium intake and quadriceps strength[310].

Diet

The primary nutrients in the treatment and prevention of osteoporosis are calcium and vitamin D, and no consistent association has been found between other dietary factors. There is a plethora of epidemiological data accumulated (64 out of 86 observational

studies) on the relationship between calcium intake in children; young adults; postmenopausal women and BMD[311]. A review of 16 observational studies assessing hip fracture and calcium intake found that an increase in usual calcium intake of 1000 mg/day was associated with a 24% reduction in the risk of hip fracture[312]. Vitamin D levels have been shown to be positively correlated with BMD in independent living men and women aged over 80 years in Sweden[313]. Osteoporosis has been linked to excessive caffeine ingestion, which has a calciuric effect, and a high intake has been associated with decreased cortical bone thickness and higher fracture rates in postmenopausal women[314].

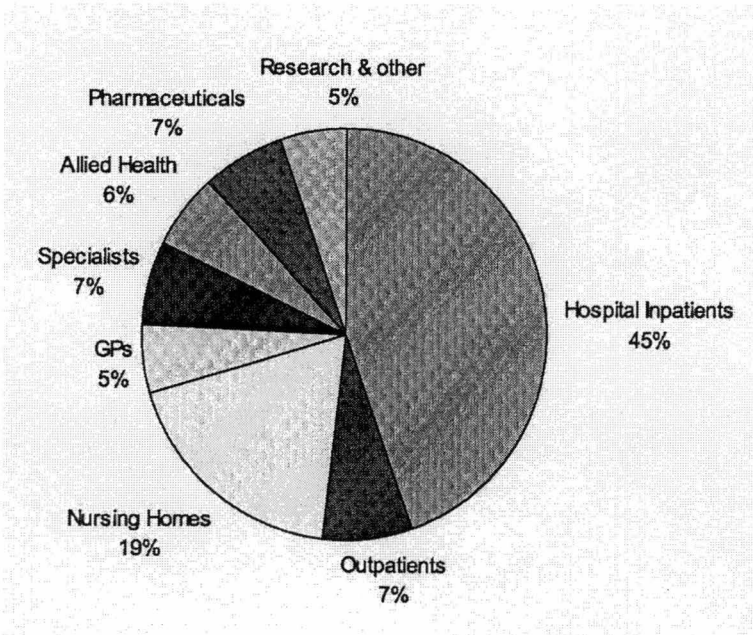
Economic costs of osteoporosis

There are three types of costs associated with conditions such as osteoporosis (direct, indirect and non-financial). Direct costs to the Australian health system include the costs of running hospitals and nursing homes, GP and specialist services, medications and allied health services. Indirect costs tend to be borne primarily by people with the disease and those who care for them. These include the income forfeited due to sickness and early retirement, equipment and devices that are required to help cope with the illness, and the cost of care, which is often provided on a voluntary basis by a spouse or other family member. Non-financial costs from loss of health are also important – the pain, suffering and premature death that results because of the disease. This is difficult to measure, but can be analysed in terms of years of healthy life lost, both quantitatively and qualitatively[183].

The financial costs associated with osteoporosis are considerable. A comprehensive costing of osteoporosis in Australia was published in 2001. Total costs

relating to osteoporosis are currently estimated at $Aust 7.4 billion, of which $1.9 billion are direct costs with hospital and nursing homes carrying the largest burden (68%)[183]. Figure 20 shows the distribution of direct health costs in Australia due to osteoporosis. There is a further $5.6 billion (conservative estimate) in indirect costs – lost earnings, volunteer carers, modifications and equipment. People with osteoporosis make modifications to their homes and purchase a variety of aids specifically designed to maximise independence and quality of life, ranging from grab rails to hip pads and walking frames. Studies in the United States have estimated the cost of these modifications and devices to be 4.4% on top of direct costs. Using this estimate, In Australia for 2000-01, the indirect cost of equipment and devices was $81.7 million, or approximately $43 per person with osteoporosis per annum[183].

Figure 20 Sectoral shares of osteoporotic direct costs, 2000-01 (Australia)[183]



Cost estimates in Australia are comparable to Europe and the United States. It has been estimated that fractures in the United States could cost as much as $US 20

billion per year, with hip fractures accounting for over a third of the total.[182]. A study on health-care expenditure attributable to osteoporotic fractures was conducted in 1995 and found that osteoporotic fractures cost the United States $US 13.8 billion in 1995[186]. In England, hip fractures alone consumed 20% of all orthopaedic beds, at a direct cost of almost £1000 million per year, in 1999[315].

Osteoporosis is so common that an individual clinical decision to intervene or not in specific patients has, in aggregate, enormous economic consequences. For example, treating all 35 million postmenopausal women in the United States with HRT would cost $US 15 billion annually, matching direct medical expenditure for treatment of the fracture themselves. The best way to balance the benefits of treatment with the potentially ruinous treatment costs remains uncertain. For example, whether or not any treatment programme at menopause is cost-effective is difficult to ascertain, because the therapy must be continued for many years when the risk of fracture is low[182]. However, using costs and criteria applicable to the United States, pharmacological treatment that reduces the risk of hip fracture has been shown to be cost-effective in high-risk individuals[316]. A recent review also concluded that several studies indicate that some interventions may be cost-effective in high-risk groups[317]. It is unfortunate that in many countries (including Australia), widespread use of medications for prevention of fractures may not be affordable for many patients at high-risk for fracture, due to the non-subsidy by governments because of high cost[182].

A recent study using a budget-impact model by Mullins *et al*[318] suggested the annual cost of long-term postmenopausal osteoporosis prevention therapy is highest during the first few years of therapy. Furthermore, long-term prevention does not provide a return on investment in fewer than 3 years, but savings in medical costs partially offset intervention costs after 2 years. For postmenopausal women,

pharmacological interventions with multiple benefits (e.g., raloxifene reducing risk of breast cancer and fracture risk) tend to be more cost-effective than interventions with a single source of health benefit[318]. Johnell *et al*[319] concluded that treating older osteoporotic women with alendronate was more cost-effective than treating younger women with osteoporosis, and treating osteoporotic women with prior spine fracture was more cost-effective than treating osteoporotic women without prior spine fracture. Risedronate also appears to be cost-effective in the elderly with and without vertebral fractures[320].

Osteoporosis in men

Osteoporotic fractures occur in about 28% of men over 60 years[321], and is a neglected area of men's health with less than 10% of men with osteoporotic fractures currently receiving anti-fracture therapy[209]. In fact, nearly 30% of hip fractures occur in men[197]. While fractures tend to occur in elderly men with multiple co-morbid disorders, secondary underlying causes of osteoporosis are common and need to be excluded. Up to 16% of men with spinal fractures have evidence of hypogonadism, with chronic smoking, excessive alcohol use, corticosteroid therapy, malabsorption and underlying bone marrow malignancies also important risk factors for osteoporosis that need to be identified[209].

Suitable diagnostic cut-off values for men are less well defined than for women[205]. No professional organisation has published consensus guidelines for osteoporosis screening in men, although experts in the field of osteoporosis have made recommendations[279]. The WHO criteria for the densitometric diagnosis of osteoporosis only apply strictly to white postmenopausal women. However, in men, declining BMD

and T-scores correlate with an increased risk of hip and other fractures similar to that occurring in women[279]. Currently, no uniformly agreed-on T-score has been established to define denistometric diagnosis of osteoporosis in men[197]. Men with T-score that are 2.5 SD below the reference mean are at substantially increased risk of fracture and should be given treatment[197]. Those men at highest risk are shown in Table 24. Treatment options for men are limited due to fewer trials but include calcium and vitamin D, bisphosphonates, PTH and testosterone if hypogonadism is present[197, 209].

Table 24 Risk factors for osteoporosis in men[197]

High risk causes

- History of nontraumatic fracture (hip, vertebrae, or wrist)
- Osteopaenia seen on plain radiograph
- Corticosteroid use of ≥ 5 mg/day for longer than six months
- Hypogonadism
- Hyperparathyroidism

Medium risk causes

- Anticonvulsant drug use (phenytoin)
- Excess alcohol consumption
- Tobacco use
- Rheumatoid or other inflammatory arthritis
- Multiple myeloma or lymphoma
- Hypothyroidism or hyperthyroidism
- Conditions associated with increased risk of falling (nursing home residence, dementia, prior fall, gait disorder)
- Family history of osteoporosis

Infrequent causes

- Cushing's disease
- Chronic liver or kidney disease
- Low body mass index
- Pernicious anaemia
- Gastric resection

Underrecognition and undertreatment of osteoporosis

As previously stated, osteoporosis represents a significant public health problem due to the morbidity, mortality and financial cost associated with fractures, and in particularly, hip fractures[183, 186, 225]. However, despite effective treatments available to reduce risk, studies have shown that osteoporosis is often under-recognised and therefore undertreated in men and women[35-52]. The underrecognition and undertreatment has been attributed to both lack of physician awareness and patients' willingness to accept treatment, if offered[322, 323].

Results from the National Osteoporosis Risk Assessment (NORA), the largest study of osteoporosis conducted to date in the United States (of over 200,000 postmenopausal women) found that almost half of the 163 979 participants with follow-up information had previously undetected low BMD, including 7% with osteoporosis[47].

There is also evidence to suggest that many patients with prior fractures do not receive treatment. In one of the largest studies (conducted in Australia) to examine the relationship between hip fractures and treatment patterns following prior osteoporotic fracture, Port *et al*[40] found that of the 348 hip fractures, 45% of women and 30% of men had a known prior fracture, including prior hip fracture in 19% of the women and 8% of the men. Among the subjects with prior fractures, only 18% of women and 7% of men were on any specific anti-osteoporosis therapy. Worse still, only 21% of women and none of the men with a prior hip fracture were taking appropriate therapy.

Another recent study highlighted the undertreatment of osteoporosis, particularly in men recently discharged from hospital following hip fracture[41]. At hospital discharge, 4.5% of men had treatment of any kind for osteoporosis, compared with 27% of women. At 1- to 5-year follow-up, only 27% of men and 71% of women were taking treatment of

any kind for osteoporosis. Of those treated, 67% of men and 32% of women were taking calcium and vitamin D only.

A study of 2804 subjects who sustained fractures found that only 4.6% had treatment initiated after the fracture[49]. Approximately 51% of women and 95% of men in the study population were not evaluated or treated in accord with guidelines or expert recommendations. The authors concluded that evaluation and treatment rates for osteoporosis in older individuals with fractures fall far below national recommendations, especially for men, and intervention strategies should be developed and evaluated to prevent refracture[49]. Another study, conducted in Italy, also found that among patients discharged from hospital, osteoporosis is an uncommon diagnosis. Even when the diagnosis is made, osteoporosis medications are often not prescribed, and treatment is reserved for younger and less medically complex patients[48].

In the Netherlands, Panneman *et al*[42] assessed the proportion of patients treated with anti-osteoporotic drugs during the 1-year period after hospitalisation for a fracture, and the influence of a guideline in the period 1998-2000 on the likelihood of receiving treatment for osteoporosis after a fracture. The majority of these patients were women (73%), and had femur fractures (51%). In total, 247 out of 1654 patients (15%) were prescribed anti-osteoporotic drugs within 1 year after discharge from the hospital. Of these 247 patients, 86 were newly treated, mainly with bisphosphonates in the year after discharge following the fracture, yielding a new treatment rate of 5%. Hence, despite the introduction of an osteoporosis treatment guideline recommending treatment for fracture patients, the majority were not being treated for osteoporosis[42].

There have been efforts to increase the use of anti-osteoporosis therapies. For example, a study[324] was conducted to examine the effect of a fracture clinic intervention in reducing previously documented undertreatment of osteoporosis in individuals with

fragility fractures. Those patients who received the intervention were more likely to follow up with a physician and to be recommended bone density testing, but were not more likely to receive an osteoporosis treatment recommendation. The authors suggested that future interventions should incorporate assessment of patients' osteoporosis health beliefs and education about risk factors for fracture, and should be coupled with physician education to achieve optimal results[324].

Thus there is clear evidence that many patients go untreated, despite the availability of effective treatments. There is wide scope for improved therapeutic interventions to decrease fracture rates, morbidity, mortality and health care costs to the community[40, 50].

Prevention and treatment of osteoporosis

Nutrition and physical activity

In general, good nutrition is as important for the skeleton as it is for any other organ system. Epidemiological studies have indicated that higher intakes of fruit and vegetables and lower intakes of protein from meat sources leads to improved bone health as assessed by markers of bone turnover and bone density[325-327]. The effects of minor nutrients and trace metals (e.g. manganese, zinc, copper) remain unknown, although there is some evidence that they can reduce bone loss[325]. The nutritional needs for optimising bone health are generally met by a diet that provides adequate calcium and vitamin D[325].

Physical activity early in life contributes to high peak bone mass. Various activities, including walking, weight training, and high impact exercises, induce a small (1-2%) increase in BMD at some but not all skeletal sites, that returns to pre-activity

levels once the exercise is stopped. Exercise may indirectly protect individuals from fractures by reducing their risk of falls[328]. Results from controlled studies have shown that exercise can increase muscle mass and strength, and reduce risk of falls by 25% in frail elderly subjects[329]. There have been no controlled trials assessing risk of fracture and the effect of exercise.

Calcium and vitamin D

Calcium is an essential nutrient that is involved in most metabolic processes and provides mechanical rigidity to the bones and teeth. Skeletal status is often equated with calcium nutrition because 99% of the calcium in the body is stored within the skeleton. To maintain normal metabolic activity, serum calcium concentration is maintained within narrow limits (2.1-2.6 mmol/l), a process controlled by the parathyroid hormone, active vitamin D, and calcitonin, with the skeleton acting as a reserve to meet the calcium needs. Calcium balance is maintained by intake, absorption, and excretion. On average, an adult absorbs only 20% to 30% of the calcium in food or tablets, although there is variation between people[325]. Numerous factors can affect the absorption of calcium, for example dietary vitamin D deficiency and high caffeine intake (>4 cups daily). Calcium excretion can also be enhanced by a high sodium, high protein diet. Table 25 shows the recommended intake of calcium for children, men and women.

Table 25 Calcium intake recommendations[330]

Group	Optimal Daily Intake (in mg of elemental calcium)
Infant	
Birth-6 months	400
6-12 months	600
Children	
1-5 years	800
6-10 years	800-1200
Adolescents	
11-24 years	1200-1500
Men	
25-65 years	1000
Over 65 years	1500
Women	
25-50 years	1000
Over 50 years (postmenopausal)	1500
On oestrogen	1000
Not on Oestrogen	1500
Over 65 years	1500
Pregnant and nursing	1200

Calcium is an important nutrient in the prevention and treatment of osteoporosis. Although calcium supplied from dairy products is as effective as calcium supplements, supplements are necessary in many patients to achieve adequate calcium intake[331]. Calcium supplementation slows the rate of bone loss, especially in elderly women and in those with a low calcium intake. Findings from studies suggest a reduction in the frequency of fractures in patients who receive calcium supplements[332-335].

A recent review by the Cochrane Review Osteoporosis Research Advisory Group[336] found that calcium supplementation alone has a small positive effect on bone density. In addition, there is a trend toward reduction in vertebral fractures, but it is unclear if calcium reduces the incidence of nonvertebral fractures. A recent meta-analysis found that calcium supplementation reduces risk of vertebral by approximately 25%[332].

Calcium is generally prescribed as an adjunct to other medications for osteoporosis, and most clinical trials supplement patients enrolled in the active and placebo groups (500-1000 mg). Calcium supplementation of about 500-1500 mg/day is safe, although constipation may be reported. The risk of kidney stones related to increased urinary calcium excretion is not elevated in those taking supplements[328]. On the contrary, adequate dietary calcium may reduce the risk of calcium oxalate kidney stones due to the binding of oxalate in the intestines[337, 338]. The preferred time to take most supplements (except calcium citrate) is with meals, because calcium is better absorbed in an acid environment. The rate of bone resorption tends to increase at night and a few studies have indicated that calcium supplements taken at night reduce this nocturnal rise. Currently, there are insufficient data to specifically recommend night-time administration of supplements[325]. There is also insufficient evidence to support the advantage of different calcium salts[328].

Vitamin D is cutaneously synthesized after exposure to sunlight and is also obtained from diet as either ergocalciferol or cholecalciferol (Figure 21). Vitamin D is hydroxylated in the liver to calcidiol and then to the active metabolite calcitriol in the kidney. Calcitriol is the most active metabolite of vitamin D, and specific receptors are found in the kidney, intestine and bone. Its primary function is to increase active intestinal calcium absorption and thus stop PTH from increasing osteoclastic action, which would lead to a release of calcium from the bones[339].

Figure 21 Metabolism of vitamin D[340]

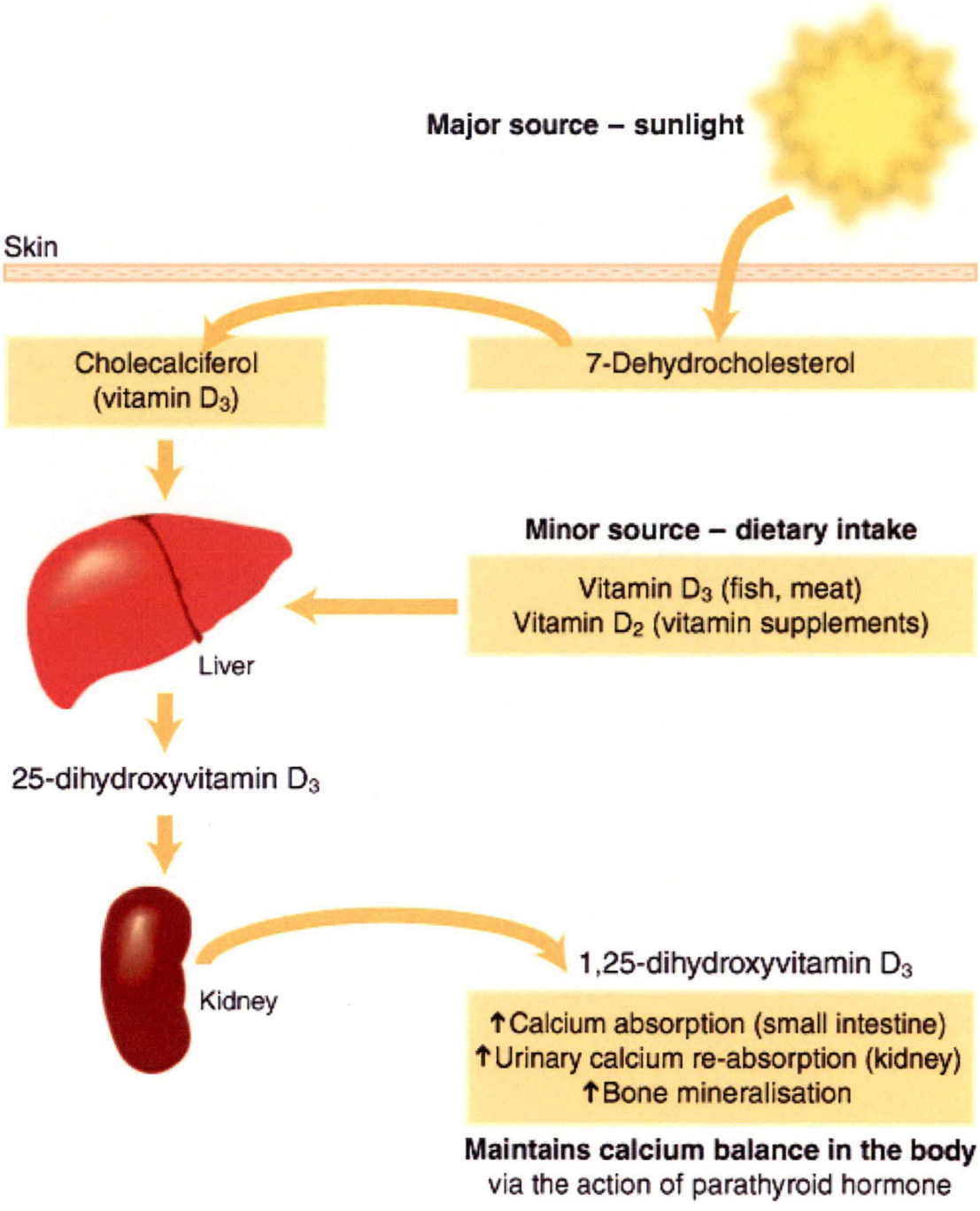


Table 26 Recommended vitamin D intake (Australia and United States)[340]

Australia (1991)
The National Health and Medical Research Council recommends that: • Pregnant women and young children receive reasonable summer sunlight exposure. • Those who are housebound or not exposed to direct sunlight for at least 1-2 hours per week should have a daily oral intake of 10 μg (400 IU) vitamin D. • Food sources of vitamin D should be included in the diets of the elderly.
United States (1997)
The Food and Nutrition Board of the Institute of Medicine of the US National Academy of Sciences has proposed the following dietary reference intakes for vitamin D: • 5 μg for those aged 0-50 years • 10 μg for those aged 51-70 years • 15 μg for those aged 71+ years (This represents a tripling of the recommended intake for those over 70 years and according to some researchers this may still be too low)

It is well established that vitamin D deficiency is often seen in patients with osteoporosis and that active vitamin D levels decline with increasing age[333, 341]. There have been several studies of vitamin D supplementation, often with calcium, demonstrating benefit on bone density[341]. Furthermore, there is very good evidence that calcium and vitamin D supplementation reduces risk of fracture[342-345].

In a French study of elderly women (mean age 84 years) who lived in nursing homes and were treated for 3 years with 1200 mg calcium and 800 IU vitamin D daily, the probability of hip and all nonvertebral fractures was significantly reduced by 29%

and 24%, respectively, compared to a placebo[343, 345]. The same results were later confirmed by the same authors approximately 10 years later[344].

Another smaller study of elderly men and women living at home also demonstrated benefit from calcium and vitamin D supplementation. There was a moderate reduction in bone loss at the femoral neck, spine, and total body over the three-year study period and a reduced incidence of nonvertebral fracture[342]. Conversely, a Dutch study of 2578 elderly but reasonably healthy women and men living independently with a high calcium intake, showed that supplementation with vitamin D (400 IU) over 3.5 years had no effect on risk of hip fracture[346]. Recently, a study demonstrated a reduction in fractures in men and women aged over 65 living in the general community who were given four monthly oral supplementation with 100,000 IU vitamin D. Total fracture incidence was reduced by 22% and fractures in major osteoporotic sites by 33%[347].

Vitamin D appears to have other benefits as well as increasing bone density. In one study, vitamin D supplementation in vitamin D deficient elderly people, improved muscle strength, walking distance, and functional ability and resulted in a reduction in falls and nonvertebral fractures. In healthy elderly people, muscle strength declined with age and was not prevented by vitamin D supplementation[348]. A study of 400 consecutive patients who attended a falls clinic found that hypovitaminosis D is very common, affecting at least 72% of the falls clinic population and that potentially all attendees at a falls clinic may be supplemented with vitamin D[349]. On the other hand, resistance exercises or vitamin D supplementation did not improve physical health or reduce falls in frail older people[350]. Vitamin D also appears to have other roles within the body, such as enhancing the immune system[340].

In summary, low calcium intake and a sub optimal vitamin D status are very common in the elderly. Evidence supports routine supplementation for these people at risk of osteoporosis as this is an effective, safe and cheap means of preventing osteoporotic fractures[351].

Bisphosphonates

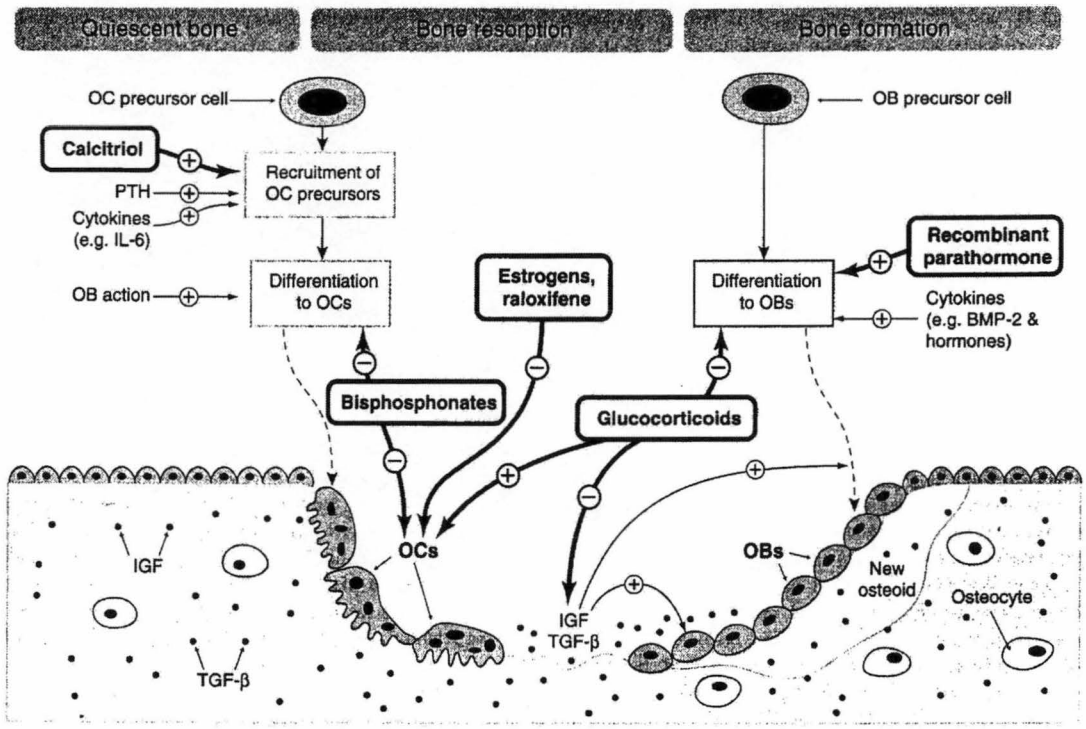
Bisphosphonates are enzyme-resistant analogues of pyrophosphate – which normally inhibits mineralisation in bone. In bisphosphonates, the P-O-P structure is replaced by P-C-P. They reduce the resorption of bone in a dose dependent manner – mainly by inhibiting recruitment and promoting apoptosis of osteoclasts (Figure 22). They also stimulate osteoblast activity. It is thought that they may be incorporated into bone matrix and ingested by osteoclasts when these resorb bone. Some bisphosphonates (e.g., alendronate, risedronate) also inhibit the mevalonate pathway, which is the same pathway responsible for cholesterol synthesis[352]. Inhibition of this pathway results in a reduction in protein prenylation by inhibition of the enzymes farnesylpryophosphate and geranylpyrophosphate. The lack of protein prenylation alters cellular function and inhibits the development of the osteoclast and causes eventual apoptosis[352].

The inhibition of osteoclast function by bisphosphonates results in a decrease in the elevated and unbalanced bone resorption seen in postmenopausal women and older men. The normalisation of the bone remodelling causes thickening of the trabecular structure and an increase in secondary mineralisation of the bone with a resultant increase in bone strength[352]. More importantly, these agents have proven benefit in reducing the incidence of fractures[209].

Bisphosphonates are also used to treat Paget's disease of the bone and hypercalcemia due to malignancy, and in some cases may reduce the risk of bone metastases caused by breast tumours[353, 354]. Oral bisphosphonates have low bioavailability (between 1-3% of dose ingested), and absorption is impaired by food, calcium, iron, coffee, tea and orange juice. Approximately 50% is deposited in the bone and 50% excreted in the urine. Bisphosphonates have a long half-life in bone of many years. Bisphosphonates have a favourable safety profile, with the most common side effect being mild-moderate gastro-intestinal discomfort[328].

Rare instances of oesophagitis have been reported with alendronate[328], and it has been reported to occur approximately one case per 1000 patient years of therapy[355]. An observational study of over 6000 men and women taking alendronate indicated that many of these gastrointestinal adverse events are not uncommon but probably related to underlying diseases and other medications rather than to the alendronate itself[356]. The risk seems to be particularly high when co-administered with nonsteroidal anti-inflammatory agents[357]. There is evidence from short term (14 days) endoscopic randomised controlled trials, that amino-bisphosphonates (risedronate and alendronate) do cause upper gastrointestinal irritation[358]. One endoscopic trial concluded that at doses used for the treatment of osteoporosis, risedronate was associated with a significantly lower incidence of gastric ulcers than alendronate[359].

Figure 22 Mechanism of action of bisphosphonates[360]



Note: IGF = Insulin-like growth factor, TGF- β = transforming growth factor-β, OC = osteoclast, OB = osteoblast

Dosing convenience is a key element in the effective management of any chronic disease, and is particularly important in the long-term management of osteoporosis. Less frequent dosing with any medication may enhance compliance, thereby maximising the effectiveness of therapy. Recently alendronate and risedronate have been made available as a once a week dose[252]. In a comparison of a once a week formulation to once daily alendronate, there were fewer serious upper gastrointestinal adverse experiences and a trend toward a lower incidence of oesophageal events in the once-weekly dosing group compared to the daily dosing group[361].

A summary of the bisphosphonates efficacy is shown in Table 27, and Table 28 provides a summary of the number of patients needed to treat, to prevent vertebral and hip fractures.

Table 27 Major fracture-prevention randomised controlled trials with bisphosphonates in postmenopausal women with osteoporosis[209]

Trial	Drug	Number of patients	Age (years)	Baseline BMD	Prior vertebral fracture (% of patients)	Duration (years)	Primary endpoint
Liberman et al[33]	Alendronate	994	45–80	LS T < –2.5	> 50%	3	BMD
Black et al[22]	Alendronate	2027	55–81	FN T < –2.1	100%	3	Vertebral fractures
Cummings et al[20]	Alendronate	4432	54–81	FN T < –1.6	0	4 2	Clinical fractures
Harris et al[34]	Risedronate	2458	Postmeno-pausal up to 85	LS T < –2	100%	3	Vertebral fractures
Reginster et al[35]	Risedronate	1226	Postmeno-pausal up to 85	~–2.7*f*	100% (all had at least 2 fractures)	3	Vertebral fractures
McClung et al[36]	Risedronate	9331	> 70	~ –3.7*	38%†	3	Hip fractures

(b) Outcomes

Trial	LS BMD (% change v placebo)	FN BMD (% change v placebo)	Vertebral fracture reduction	Non-vertebral fracture reduction	Hip fracture reduction
Liberman et al[33]	8.8	5.9	48%	21%	—‡
Black et al[22]	6.2	4.1	47%	20%	51%
Cummings et al[20]	8 3	3.8	44%	12%*	21%
Harris et al[34]	5.4	1.6	41%	39%	—‡
Reginster et al[35]	5.9	3.1	49%	33%	—‡
McClung et al[36]	—‡	2.1*	40%†	—‡	30%

f = mean * Not measured in all patients † Not assessed in all patients. ‡ Not measured BMD = bone mineral density. FN = femoral neck. LS = lumbar spine. T = T-score.

Table 28 Number-needed-to-treat (NNT) for vertebral and hip fractures for alendronate, risedronate and raloxifene[362]

Drug therapy	Vertebral fractures confirmed by x-ray* (NNT)	Hip fractures (NNT)
Alendronate		
• In women with fractures	14 for 3 years	90 for 3 years
• In women without fractures	59 for 4 years	Not statistically significant
Risedronate		
• In women with or without fractures†	9-20 for 3 years	90 for 3 years**
Raloxifene		
• In women with fractures	13 for 3 years	Not statistically significant
• In women without fractures	53 for 3 years	Not statistically significant

* There is debate as to how well radiographic measures of vertebral fractures equate to "clinical" fractures with symptomatic back pain

†Trials had mixed populations of women with and without fractures; it was not possible to analyse them separately

** This result was not statistically significant in women without existing vertebral fractures

Etidronate

Etidronate was the first bisphosphonate developed and is given cyclically as continuous use can induce osteomalacia: patients are instructed to take 400 mg for two weeks every three months. Patients should also take these tablets (with plain water only) on an empty stomach, two hours before food or two hours after food[363]. Etidronate increases lumbar spine BMD by approximately 4% with a reduction in vertebral fractures after 2 years, although this is not significant after 3 years[328]. A meta-analysis from controlled clinical trials suggested that etidronate reduces vertebral fractures by 37%, but has little effect on nonvertebral fractures[364], although increases in hip BMD have been reported from 2-4%[365].

Alendronate

Alendronate is one of the most commonly used agents for the treatment of osteoporosis[365]. Alendronate has been shown in randomised placebo-controlled clinical trials at daily doses of 5mg and 10 mg to increase BMD at the lumbar spine, femoral neck and total body in postmenopausal women. Alendronate 10 mg/day is associated with an increase in BMD of 6-9% at the lumbar spine and 2.5-6% at the femoral neck[274, 275, 366, 367]. Recent data has shown that alendronate does not have to be taken every day, and 70 mg given once a week achieves similar increases in BMD at the lumbar spine and femoral neck as 10mg daily[361], although there is no anti-fracture data available on the weekly treatment.

A randomised, double-blind, placebo-controlled, clinical trial determining whether hormone replacement and alendronate in combination are efficacious and how they compare with monotherapy in community-dwelling elderly (>65 years) women was recently completed. Alendronate was superior to hormone replacement, and combination therapy was superior to either therapy alone. It was concluded that combination therapy may represent an option for women with more severe disease or for those who have failed to achieve an adequate response to monotherapy[368].

Alendronate (and risedronate) can be used for the *prevention* of osteoporosis in postmenopausal women with low BMD[209]. In double-blind placebo-controlled trials of postmenopausal women 60 years or younger, alendronate at a dose of 5 mg/day, prevented bone loss in most women and increased mean BMD at the most sites by 1-7%[365]. A recent trial demonstrated that 35 mg alendronate given once a week was equivalent to 5 mg daily in postmenopausal women (without osteoporosis), and significantly increased BMD at all sites[369].

Alendronate has also been approved for the treatment of osteoporosis in men. Alendronate treatment in men is associated with increases in BMD of approximately 5% at the lumbar spine and 2.5% at the femoral neck[370]. Similar benefits were demonstrated in another more recent study[371]. The use of alendronate and its relationship to fracture risk in men is not completely clear[365], although it appears to reduce the incidence of vertebral fractures and reduce loss of height. These risk reductions, however, have not been shown to be statistically significant[370].

The optimum duration of treatment is unknown although data have been published on the use of alendronate for 10 years[372, 373]. Some experts suggest limiting treatment to 4 years (and monitoring BMD) as there are little data on the long-term effects of bisphosphonates[374]. There are some data suggesting accelerated bone loss is not observed when treatment is discontinued[375].

Risedronate

It has been shown that risedronate prevents postmenopausal bone loss[376]. Randomised placebo-controlled clinical trials demonstrate that risedronate, at daily doses of 2.5 mg and 5 mg increases BMD of the lumbar spine, femoral neck and radius in postmenopausal women with osteoporosis. The greatest increase is seen when the approved dose is used for treatment (5 mg/day). The average increase in lumbar spine BMD is 4-7% and the average increase in femoral neck BMD is 3%[365].

Harris *et al*[377] demonstrated that 5 mg/day of risedronate significantly reduced new vertebral fractures by 41% over 3 years in 2400 women with prevalent vertebral fractures. In another study of over 1200 women with 2 or more vertebral fractures, treatment with risedronate produced an approximate 50% reduction in new vertebral

fractures after 3 years[378]. The overall reduction in nonvertebral fractures over the 3 years was 30-40%[377, 378].

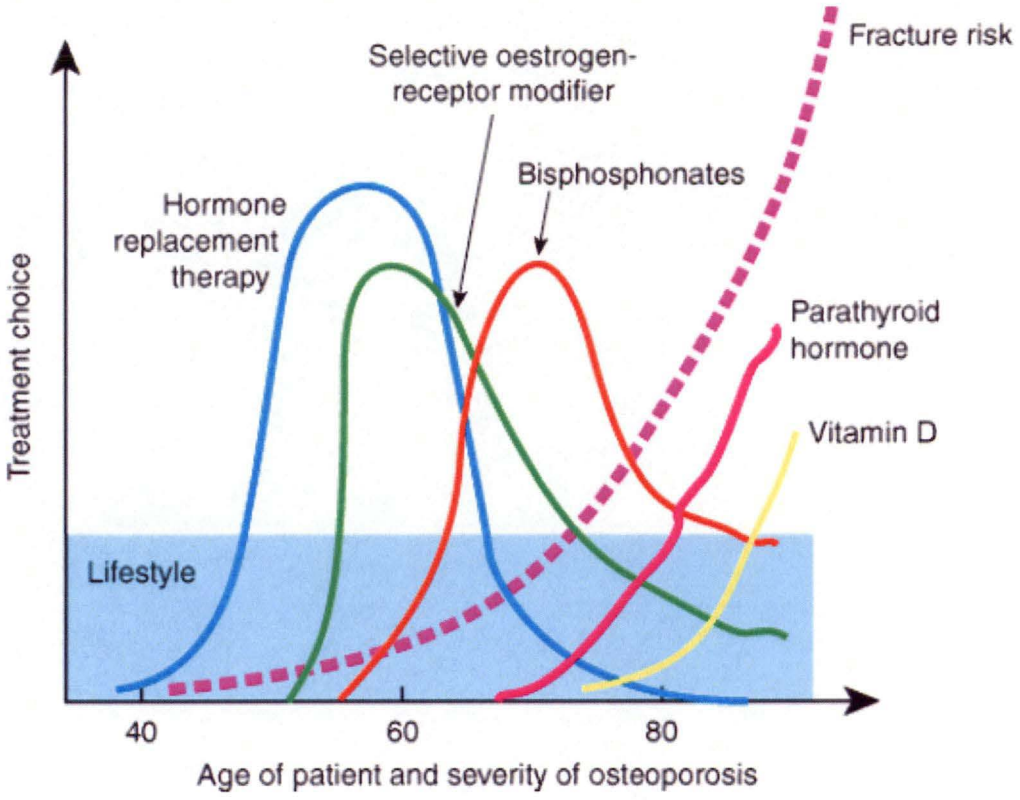
Recent data from a 1 year randomised trial showed that risedronate either given 5 mg daily or 35 mg once a week are comparable in increases in lumbar spine and hip BMD, although fracture data is not available[379]. Watts *et al*[380] recently used historical control data to show that once a week risedronate provides equal fracture prevention to the daily regimen, although prospective data are required to confirm this.

Similar to alendronate, there are little long-term data on the effects of risedronate. Recently, a 3-year placebo controlled vertebral fracture study of risedronate was extended for 2 years[381]. Increases in spine and hip BMD that occurred in the risedronate group during the first 3 years were maintained or increased with a further 2 years of treatment. The mean increase from baseline in lumbar spine BMD over 5 years was 9.3%.

Other bisphosphonates

Other bisphosphonates such as clodronate, tiludronate, pamidronate and ibandronate are used for treating malignant bone disease and Paget's disease, and may prove beneficial in the treatment and prevention of postmenopausal osteoporosis[328]. It was recently shown that zolendronate, used in malignant bone disease, given as a single annual infusion increased BMD in postmenopausal women and may prove useful in the treatment and prevention of osteoporosis. No fracture data are currently available[382]. Findings from a new study suggest that weekly ibandronate therapy is just as safe and effective as daily therapy for postmenopausal osteoporosis[383].

Figure 23 Therapeutic options in the management of osteoporosis with increasing age[384]



Selective oestrogen-receptor modulators

Selective oestrogen-receptor modulators (SERMs) are synthetic, non-steroidal agents, which bind to the oestrogen receptor, resulting in either oestrogen-agonist or oestrogen-antagonist effects in different target tissues. Tamoxifen is classified as a SERM, although it only has indications for the treatment and prevention of breast cancer since its effect on fracture reduction is not well established, as most studies have not been primarily designed to assess fracture as an endpoint, rather risk of breast cancer [385]. Tamoxifen is precluded from widespread clinical use in postmenopausal women due to the increased risk of endometrial cancer[328].

Raloxifene is another SERM that competitively inhibits the action of oestrogen in the breast and the endometrium, and acts as an agonist on bone and lipid metabolism. Its exact mechanism of action is only partly known, but it produces increascs in osteoblast activity and a decrease in osteoclast activity which collectively prevents postmenopausal bone loss at all skeletal sites and reduces markers of bone turnover[386]. Results from the MORE study (Multiple Outcomes of Raloxifene Evaluation)[387], which involved over 7000 women with osteoporosis, indicated that raloxifene 60 mg daily produced a 30% reduction in vertebral fractures in women with prevalent vertebral fractures and up to 50% in those women without prior vertebral fractures. However, despite modest increases in BMD, there was no reduction in nonvertebral fractures. This has been suggested to be due to the study population being younger and having less severe osteoporosis than patients in other trials[388].

The MORE trial demonstrated increases in BMD in the order of 2-3% for total body, hip and lumbar spine. It thus seems paradoxical that it could result in a similar reduction in vertebral fractures as the bisphosphonates, which have increases in BMD of 4-9%[386]. It has been suggested that much of the anti-fracture efficacy of raloxifene in cancellous bone is due to the normalisation of bone-turnover and thus microarchitectual disruption and not BMD changes alone, whereas in cortical bone (e.g., hip) it is necessary to increase BMD more substantially to reduce fractures[389]. The MORE trial also demonstrated that raloxifene lowers the risk of breast cancer by 76%[386], although it is unknown whether younger women at high risk will achieve similar risk reduction. Results from trials are currently awaited for evaluating raloxifene as a suitable agent for breast cancer prevention[386] and coronary heart disease[390].

Raloxifene at a dose of 60 mg/day is effective in preventing and treating postmenopausal osteoporosis. It is well tolerated, but may induce hot flushes and although rare, it can increase the relative risk of thromboembolic disease, at a similar rate to that seen with HRT[328]. As with other medications, patients are advised to maintain an adequate calcium intake (supplement if necessary) and 400IU of vitamin D is advisable[386]. Table 28 provides the number of postmenopausal women treated with raloxifene to gain benefit (reduction in fractures) from its use.

Hormone replacement therapy

There is much evidence to support a role of oestrogen in developing and maintaining skeletal integrity. Osteoblasts and osteoclasts have oestrogen receptors, and bone turnover increases when oestrogen levels fall. Oestrogen counters the formation pro-inflammatory cytokines which promote bone resorption by bone cells and reduces parathyroid hormone secretion[391]. Oestrogen stops bone loss in early, late, and elderly postmenopausal women by inhibition of bone resorption, resulting in a 5-10% increase in BMD over 1-3 years[328]. Calcium supplementation may enhance the effect of oestrogen on BMD. When HRT is ceased, bone loss resumes at the same rate as after menopause[328].

Findings from many case-controlled and cohort studies suggest that HRT decreases the risk of hip fracture by 30%, and placebo controlled studies suggest a 50% reduction in spinal fractures[328]. Two meta-analyses[332, 392] suggested that HRT reduces vertebral fractures by approximately 35%, while another meta-analysis[287] found that HRT reduced nonvertebral fractures by 27% - with a 40% reduction in risk of hip fracture. Cranney *et al*[332] found only a 13% and insignificant reduction in nonvertebral

fractures with HRT use. There have been no placebo controlled trials of HRT in women with osteoporosis and with incident fractures as a primary endpoint[328].

The Heart and Estrogen/Progestin Replacement Study (HERS) was a randomised, double blind, placebo-controlled secondary prevention trial of combined HRT on the occurrence of non-fatal myocardial infarction or coronary heart disease death among women with documented heart disease. Fractures were a secondary endpoint and there was no evidence that HRT substantially reduced the incidence of fractures or height loss among older, non-osteoporotic women[393, 394].

Hormone replacement therapy has also been suggested to have beneficial effects on coronary heart disease and cognitive function[328]. However, the recent publication of the WHI study of over 16000 postmenopausal women randomised to HRT or placebo, demonstrated that HRT increased the risk of breast cancer[290] and stroke[290, 395]. Furthermore, combined HRT did not prevent mild cognitive impairment in these women[396]. However, the WHI did show that combined HRT significantly increased BMD by 4% and significantly reduced the risk of all fractures by 24%. There was a reduction in hip and vertebral fracture of 34%, but when considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit, even in women considered to be at high risk of fracture[291]. The WHI also demonstrated a 37% reduction in colorectal cancer risk[291]. The recent Million Women Study[397] also confirmed the increased risk of breast cancer with HRT use, particularly with current use and oestrogen-progesterone combinations.

The results from these major studies question the role of HRT in the prevention of postmenopausal osteoporosis. HRT had been widely accepted as the treatment of choice for the management of menopausal symptoms. However, the WHI and other recent randomised controlled trials have failed to confirm beliefs of other potential

benefits in reducing the risk of coronary artery disease and stroke. The use of HRT has been suggested for short-term therapy for symptom management with treatment individualised for each woman[398].

It has been argued that HRT still remains the first option for preventing fractures in symptomatic postmenopausal women[399]. In women at risk of osteoporotic fracture, therapy should be individualised, and use of HRT to prevent osteoporosis may be appropriate in symptomatic women, but individual benefits should be weighed against the potential increase in breast cancer with long-term (> 5 year) use. In women with osteoporosis, the benefit of a reduced fracture rate with long-term combined HRT must now be balanced against the increased risks of breast cancer, stroke, heart disease and thromboembolism[400].

It must be emphasised that the WHI trial examined only oral HRT with conjugated oestrogens and medroxyprogesterone acetate. However, the oestrogen only arm of the WHI was also recently ceased prematurely due to an increase in strokes in the oestrogen users[401]. It is not yet known whether other oestrogens and progestins, tibolone, or HRT delivered by non-oral routes have different effects[399].

Calcitonin

Calcitonin, produced by the thyroid, reduces bone resorption by direct inhibition of osteoclast activity. Calcitonin's effect on bone has been demonstrated in small studies measuring BMD, although there is limited data on its ability to reduce fracture. There have been no randomised-controlled trials with injectable calcitonin using vertebral fracture as an endpoint. There are no data on the efficacy of injectable calcitonin on nonvertebral fracture[402]. There are data to support the use of a nasal spray formulation of

calcitonin. The PROOF study[403], a 5-year double-blind randomised placebo controlled study of 1255 postmenopausal osteoporotic women, showed that intranasal calcitonin 200 IU a day reduced vertebral fractures by 30%. There was no significant reduction in nonvertebral fractures. However, 60% of patients were lost at follow-up in this study.

Anabolic agents

Testosterone

Testosterone has not been widely studied for the treatment of osteoporosis and there are limited data on fracture outcomes. In general, anabolic steroids produce increments in BMD similar to oestrogens or other antiresorptive agents[404]. Further studies are required to confirm the safety and efficacy of testosterone treatment in eugonadal men with osteoporosis[405].

Parathyroid hormone

The United States Food and Drug Administration (FDA) recently approved teriparatide, recombinant human parathyroid hormone 1-34 (PTH), for the treatment of osteoporosis in high-risk patients. Patients considered to be at high risk for fracture include those who have failed on or proved to be intolerant of previous osteoporosis therapy[406].

Teriparatide is an anabolic agent that works primarily to produce new bone by increasing the number and action of osteoblasts. Unlike other currently approved osteoporosis therapies, which are classified as antiresorptive agents, teriparatide is classified as a bone formation agent. It is identical in structure to amino acids 1-34 in the active portion of human PTH and thus induces the same effects as endogenous PTH[407].

Teriparatide stimulates both osteoblast and osteoclast function, and the effect on the skeleton depends on the pattern of exposure. Once-daily or intermittent administration of teriparatide results in new bone formation by preferentially stimulating osteoblast activity over osteoclast activity, leading to a net balance in favour of bone formation. Continuous exposure to endogenous PTH may produce detrimental effects on the skeleton because osteoclast activity and bone resorption may predominate[406].

The largest study involving 1637 postmenopausal women with prior spinal fractures found that new spinal fractures occurred in 14% of placebo-treated women versus 5% of women treated with 20 mcg teriparatide. Teriparatide increased BMD by 9% in the spine and 3% in the hip over and above the control group. In addition, teriparatide also reduced spinal fracture risk by 65% and non-spinal fractures by 55%[407]. Teriparatide has also been shown to increase lumbar spine and femoral neck BMD in men[408]. The latter study was stopped after a median duration of 11 months because of a finding of osteosarcomas in rats in routine toxicology studies[408].

The use of PTH in combination with other therapies has proven disappointing[409, 410]. For example, a study [409] found that alendronate impairs the ability of PTH to increase the BMD at the lumbar spine and the femoral neck. They postulated that this effect might be attributable to an attenuation of PTH-induced stimulation of bone formation by alendronate. In another randomised, double-blind clinical study of PTH and alendronate in women, there was no evidence of synergy between parathyroid hormone and alendronate[410]. An earlier study found that alendronate did not block the anabolic effect of PTH, although the sample size was small (n=10)[411].

Teriparatide is currently only recommended for patients with the most severe form of disease. Most prominently, teriparatide was shown to increase risk of osteosarcoma in rats, although no cases have been reported in humans taking this

medication. Currently, the drug is only recommended to be used for 2 years maximum[406]. Other potential reasons that teriparatide should be reserved for patients with more severe disease include its cost ($US 7000/year) and that it requires daily subcutaneous injection.

Others

Strontium is under development for the treatment for postmenopausal osteoporosis. Early experimental work has shown that strontium inhibits bone resorption and may stimulate bone formation[328]. A Phase III study by Meunier *et al*[412] showed that 3 years strontium treatment (2 g/day) in postmenopausal women produced a mean of 14% increase in lumbar BMD which was significantly higher than placebo and was associated with a 41% reduction in new vertebral fractures. In addition, hip BMD increased by 8%, which was significantly higher than the placebo arm of the trial. These findings support earlier research by Reginster *et al*[413] who found at 2 years of therapy, strontium 1 g/day significantly increased lumbar BMD compared with placebo with an overall beneficial of about 2.4%. Femoral neck and total hip BMD were also significantly increased at 2 years by, 2.5% and 3.2%, respectively.

Observational studies have shown an association between vitamin K status and risk of hip fracture in postmenopausal women[414]. Treatment in 241 Japanese osteoporotic patients with vitamin K2, demonstrated improved lumbar spine BMD compared to the control group[415]. Another study using vitamin K1 supplementation with co-administered minerals in healthy postmenopausal women demonstrated a retardation of bone loss at the femoral neck[416].

The results of a meta-analysis indicated that current thiazide users have a 20% reduction in fracture risk and that long-term use may reduce fractures by a similar amount[417]. A prospective population-based cohort study of 7891 individuals 55 years of age and older where 281 hip fractures occurred, studied the relationship between thiazide use and fracture. Relative to non-use, current thiazide use for more than 365 days was statistically significantly associated with a 54% lower risk for hip fracture (95% CI, 0.21 to 0.96). This lower risk disappeared approximately 4 months after thiazide use was discontinued[418]. Although thiazide diuretics reduce tubular reabsorption of calcium and perhaps decrease bone turnover, their role in the management of osteoporosis has not been established[328].

Recent studies suggest that the mevalonate pathway plays an important role in skeletal metabolism. HMG CoA reductase inhibitors ("statins"), which inhibit a key enzyme in the mevalonate pathway, are widely used for the treatment of hyperlipidaemia. In vitro and animal studies demonstrate that "statins" stimulate the production of BMP-2, a potent regulator of osteoblast differentiation and activity, suggesting that "statins" may have an anabolic effect on bone. "Statin" use in most, but not all observational studies is associated with a reduced risk of fracture, particularly hip fracture, even after adjustment for the confounding effects of age, weight and other medication use. Further studies of the skeletal effects of "statins" are required, to determine the optimal formulation, dosing, and route of administration. Clinical trials with fracture endpoints are required before "statins" can be recommended as therapeutic agents for osteoporosis[419, 420].

When administered, fluoride is incorporated into the hydroxyapatite of bone, and stimulates osteoblast activity and thus increases bone formation. In humans fluoride increase spinal BMD, with little effect on hip BMD. Because there is some evidence that

it has may have an adverse effect on hip fractures, fluoride is not currently recommended for postmenopausal osteoporosis[328]. Excessive intake over a long period of time has been associated with fractures[404].

Other agents that have undergone some clinical trials as new or alternative drugs for the treatment of osteoporosis include growth hormone and insulin-like growth factor-1. The targets/drugs that are being developed to inhibit bone resorption include the OPG/ RANKL/RANK system[421].

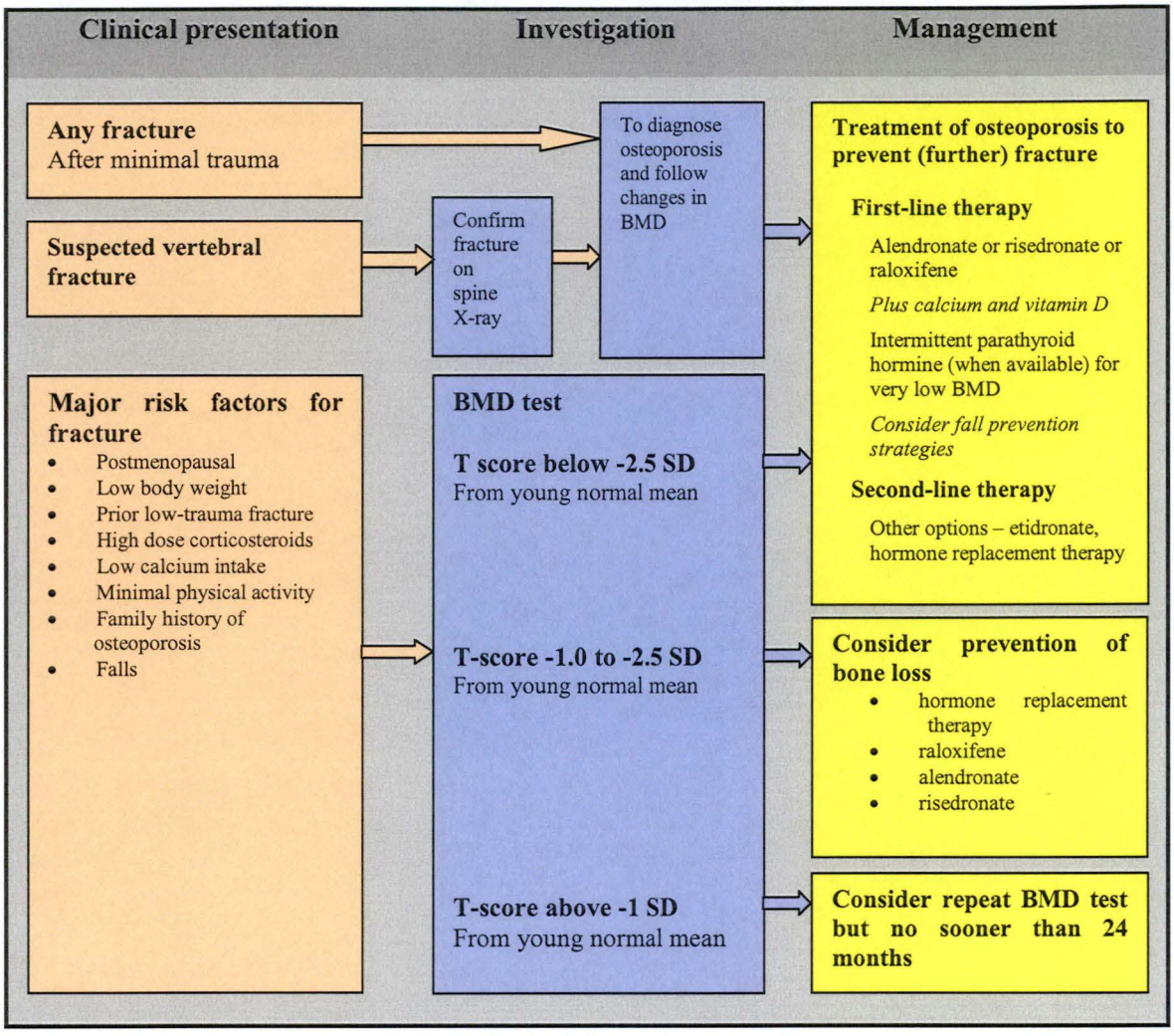
Summary of treatment options

A summary of treatment options along with with usual doses and adverse effects are shown in Table 29 and a current algorithm for the treatment of investigation and management of osteoporosis in Australia is shown in Figure 24.

Table 29 Pharmacotherapy for osteoporosis currently available in Australia[363]

Drug	Usual dose	Adverse effects and contraindications
Bisphosphonates • *alendronate* • *risedronate* • *etidronate*	10mg daily; 70 mg weekly 5 mg daily; 35 mg weekly 400 mg daily for 2 weeks every 3 months	*Common:* nausea vomiting, diarrhoea, musculoskeletal pain. *Infrequent:* oesophagitis, oesophageal erosions and ulcers. *Contraindications*: oesophageal disorders or inability to stand or sit upright for 30 minutes after drug administration. *Note:* Drug must be taken with plain water only to be adequately absorbed.
Selective oestrogen receptor modulators • *raloxifene*	60 mg daily	*Common:* hot flushes, sweating, leg cramps. *Infrequent:* deep vein thrombosis, pulmonary embolism
Calcium	Adjust according to individual requirements	Hypercalcaemia, constipation
Simple Vitamin D • *ergocalciferol* • *cholecalciferol* **Active vitamin D** • *calcitriol*	400 – 800 IU daily 400 – 800 IU daily 0.25 mcg twice a day	Most adverse effects are due to effects of hypercaleamia. Early symptoms include nausea, vomiting, constipation, sweating, polyuria. *Note:* ergocalciferol only available as a 1000 IU capsule
Hormone replacement therapy	Adjust according to preparation and individual requirements.	*Common:* mastalgia, breakthrough bleeding, spotting, dry eye syndrome, change in libido. *Infrequent:* fluid retention, oedema, and weight change. *Rare:* gallstones, stroke, deep vein thrombosis, and pulmonary embolism, increase risk of breast cancer. *Note:* only use if patient is deficient in sex hormones

Figure 24 Algorithm for treatment of osteoporosis in postmenopausal women[209]



Part II (a): Evaluation of pharmacist performing osteoporosis screening in rural pharmacies using quantitative heel ultrasound

Chapter 1: Introduction

Background

Osteoporotic fractures and their complications are associated with high health care costs. As the incidence of osteoporotic fractures, particularly hip fractures, increases with advancing age, the greatest costs in terms of health care expenditure and loss of quality of life tend to occur in the elderly[177]. Of those Australians over 60 years of age, 1 in 2 women and 1 in 3 men will sustain an osteoporotic fracture[209]. There is evidence that osteoporotic fractures that occur in rural Australians have a higher hospitalisation rate than those living in metropolitan areas[422], although rural people tend to have a lower fracture rate than metropolitan people[219, 223].

As the disease has no manifestations prior to fracture, strategies to reduce its personal and economic burdens require measurement of bone mass in the population most likely to be affected. Low BMD is the best predictor of fracture risk. A variety of techniques are available to measure BMD, including single energy X-ray absorptiometry, quantitative computed tomography, and quantitative ultrasound

(QUS)[205]. The gold standard, however, is dual energy X-ray absorptiometry[205, 209]. Unfortunately, relatively few individuals have access to the more expensive, stationary DEXA used to measure central (hip and spine) bone mass. Therefore, measurement of peripheral (e.g. heel) bone density by inexpensive, portable units is necessary to meet the need for broader testing of the population. This is of particular importance in rural populations as they generally have less access to preventive health services in general[423].

There is good correlation between QUS parameters and bone density of the calcaneus with correlation coefficients of between 0.6 and 0.8 found[424]. Calcaneal QUS measurements have been shown to predict fracture risk[205, 214, 425]. Osteoporosis screening in patients with strong risk factors in community pharmacies is feasible, given such pharmacies' accessibility to patients, stable presence in the community, and staff pharmacists' relationships with patients and other primary health care providers[426-428]. Although peripheral bone density measurement devices have been used at pharmacies and other venues, there are very few published reports worldwide on programmes involving their use[426, 428].

Quantitative ultrasound (QUS)

Quantitative ultrasound is a new non-invasive technique used to assess skeletal health[429-431]. QUS has many advantages over X-ray based densitometry in that it is more portable, non-ionising, less expensive and often faster, as well as having potential for mass screening.

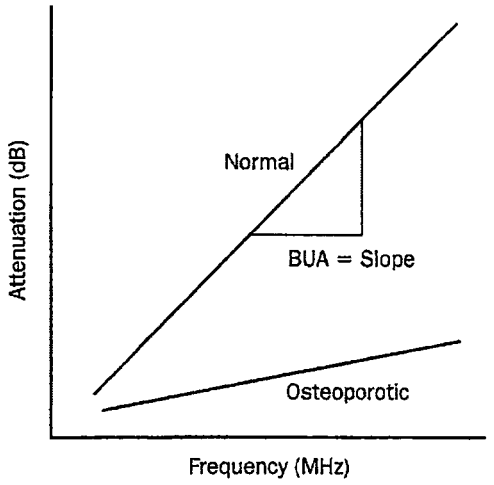
Ultrasound refers to sound waves of frequency greater than 20 kHz. Sound (ultrasound) represents a mechanical disturbance propagating through a medium, where velocity and attenuation of the wave are related to the physical properties of the medium,

in this case - bone. The mechanical properties of the medium progressively alter the shape, intensity (energy per second per unit area) and speed of the propagating wave. In QUS, longitudinal ultrasonic wave is passed through an appendicular skeletal site, and the resulting changes in the ultrasonic wave relate to both the structural/mechanical properties of the bone and its mineral content[431, 432].

Two fundamental parameters are routinely derived form ultrasound measurements– speed of sound (SOS) and broadband ultrasound attenuation (BUA). Speed of sound refers to the distance travelled per unit time, expressed in metres per second. The homogeneity of healthy bone promotes sound transmission. Thus, the speed of sound transmission is higher in healthy bone and lower in osteoporotic bone[431, 432].

The second wave characteristic, BUA, expressed as decibels per megahertz (db/MHz), is defined as energy loss occurring as an ultrasound beam traverses a medium. Healthy trabecular bone is a highly attenuating medium because it scatters sound waves. To traverse bone tissue, lower frequency sound waves must be used because attenuation is linearly proportional to frequency. Waves are transmitted at multiple frequencies throughout wave frequencies of 0.2 to 1.0 MHz and the attenuation quantified. The slope of attenuation as a function of frequency is known as broadband ultrasound attenuation. Compared with healthy bone, osteoporotic bone is less attenuating and BUA values are lower (Figure 25)[431, 432].

Figure 25 Description of BUA measurement where attenuation is a function of ultrasound frequency (BUA is the slope of the regression line)[433]



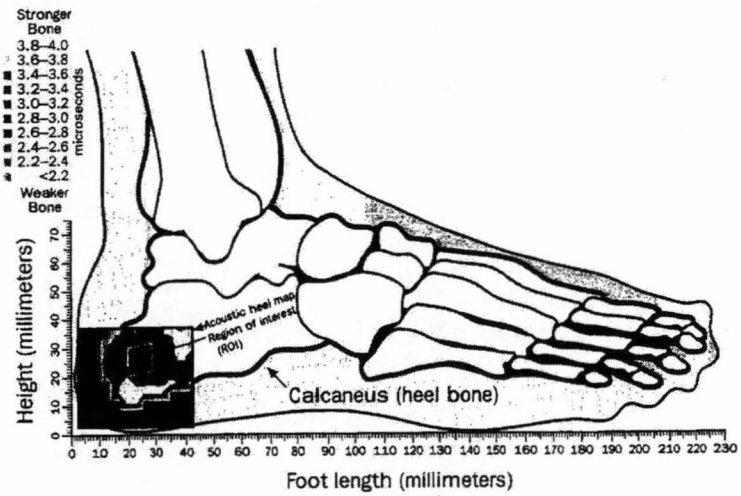
In many systems, the characteristics of SOS and BUA are combined to give a single measure. For example, the Sahara machine reports the quantitative ultrasound index (QUI). It is claimed that these indices improve coefficients of variation, and therefore, precision. These measures are then compared with reference ranges and reported as T-scores[432].

The heel, rather than the finger, phalanges or tibia, is the preferred QUS measurement site, for several reasons. Firstly, the heel comprises 95% trabecular bone, which undergoes rapid change compared to cortical bone; measurement should therefore detect early signs of metabolic change. Secondly, QUS calcaneal measurements show a high correlation with DEXA calcaneal BMD ($r = 0.8$). Thirdly, the heel has been previously established as an optimal site for predicting fracture risk[431].

QUS systems

Since the early work of Langton *et al*[434] in 1984 many clinical quantitative ultrasound machines have been developed. Ultrasound transducers are coupled to the subject either with water (wet system) or gel (dry system). The sites measured also vary, but the majority of the systems measure the calcaneus. There are a number of wet systems available and there is little to choose between the various devices in terms of clinical perfomance[435].

Figure 26 Site for measuring calcaneal bone characteristics[436]



Clinical QUS gel-coupled (dry) systems do not use water as a coupling agent. Instead, sound energy is conducted to and from the ultrasound transducers through a thin layer of water or oil-based gel applied to the skin of the heel before the test. There are numerous gel-coupled devices available, including the Sahara Clinical Bone Sonometer (Hologic Inc., Bedford, MA, United States). Compared with water-coupled systems, gel-coupled systems have the advantage of being more portable and having fewer potential

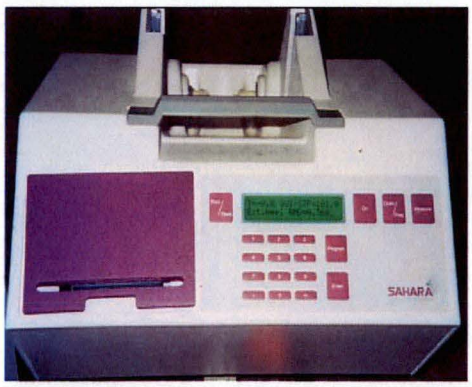
concerns about hygiene. Disadvantages result from their reduced control over the measurement environment, such as the stability of the temperature and hydration of the tested heel. These factors can potentially affect the precision of the measurements [436]. Until there is an accepted standard for ultrasound measurement, the results obtained on one device cannot be directly compared with those from another, even when both claim to deliver the same measurement (e.g. BUA, SOS, etc)[436]. Studies have attempted to address this issue and provide guidelines for various devices[437, 438].

Sahara clinical bone sonometer

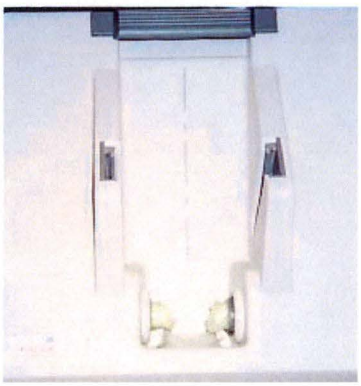
The Sahara device (Figure 27) is a gel-coupled contact heel ultrasound and was the first QUS device to be approved by the United States FDA. The Sahara has two single-element, 19-mm diameter transducers that are mounted on a motorised calliper mechanism and are coupled to the heel via soft elastomer pads and a coupling oil gel. The pads are placed in direct contact with the patient's skin. A rigid foot-positioning device is provided to ensure reproducibility of leg and foot position during data acquisition. The output variables for the Sahara are: BUA, SOS, estimated heel BMD and quantitative ultrasound index (QUI, obtained from measured BUA and SOS)[436].

Figure 27 The Sahara Clinical Bone Sonometer (a) front panel; (b) aerial view (c) patient preparation (d) patient positioning

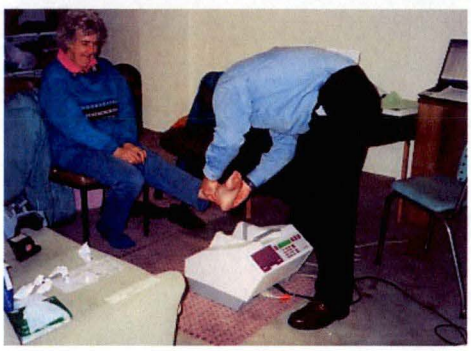
(a)



(b)



(c)



(d)

While ultrasound does not measure BMD directly, some clinical studies have shown that the Sahara ultrasound results are highly correlated to BMD of the heel ($r = 0.85$) as measured by DEXA. Hence the Sahara device is useful to use to estimate heel BMD[436, 439].

Error sources in QUS

The accuracy of a method (i.e., the agreement of measured and true data) determines its ability to discriminate between healthy and osteoporotic subjects or to assess fracture risk. The most relevant error sources of QUS measurements for clinical application are summarised in Box 2.

Box 2 Error sources for QUS measurements[440]

1. System performance: stability, aging of pads, and quality of water bath.
2. Positioning: measurement of anatomically consistent regions, sequential repositioning.
3. Soft tissue impact: oedema, temperature of foot.
4. Coupling of the sound to the skin: air bubbles, wetting of skin.

System performance should be monitored using phantom-based quality assurance procedures. Whether or not a cross-calibration between different types of devices is possible remains to be evaluated in the future. Positioning errors can potentially be minimised by using images for the definition of the proper 'region of interest'. A careful preparation of the skin according to the manufacturer's recommendation is very important for sufficient precision[440]. Foot positioning is considered the primary source of error in BUA measurement because of the lack of homogeneity of the calcaneous[441].

Quality assurance and quality control in QUS

An accepted method of monitoring equipment performance is to measure parameters of interest using a test object. The test object (phantom) attempts to emulate the in-vivo measurements as much as possible in terms of geometry and acoustic properties. A phantom is generally considered valuable in quality control efforts because it more closely represents the actual measurement. Manufacturers provides a phantom for quality control purposes[442].

Achieving high precision when using quantitative ultrasound is essential in patient assessment and poor precision can be minimised by the following steps shown in Box 3.

Box 3 Essential protocol to achieve high precision when using QUS in clinical practice[442]

1. All personnel should be well trained by the manufacturer
2. Use stringent measurement protocols, including foot straps where appropriate
3. Scrub the heel well prior to submersion in water or application of the gel
4. For dry systems apply the gel generously to the measurement area
5. Monitor the phantom results weekly to identify drift
6. Store the phantom in a stable temperature environment near the scanner
7. Maintain constant room temperature, especially for wet systems without temperature control

One aspect of quality assurance in DEXA testing is the qualitative examination of the scan image. However, most QUS machines do not provide images, and the operator must rely on other means to assess the quality of the signal. Hologic (Hologic Inc., Bedford, MA, USA) has implemented a quality control (QC) check on the calculation of BUA with the Sahara scanner. One parameter reported by Hologic is the quantitative ultrasound index (QUI), a composite parameter of BUA and SOS. If the BUA values are suspect, the QUI is marked with an asterisk. The asterisk indicates that the BUA value used to determine the QUI is actually an estimated BUA result predicted

by SOS (BUA and SOS are moderately correlated). Other devices also give a warning signal if the quality of the result is suspect or low[442]. By evaluating the quality of the examination, repeat measurements can be obtained immediately when a problem is detected.

QUS also suffers from technical problems that do not appear to be replicated with other bone mass measurement technologies. For example, dry systems (as used in this study) in particular may give falsely low readings in patients with peripheral oedema and this will adversely affect precision for follow-up measurements, as well as producing falsely high fracture algorithm. A further problem is temperature dependency, which may be partly mediated by the ambient temperature of the room, but is also dependent on heel temperature. Care must be exercised therefore in using the technology in environments with variable temperature and repeated measurements should be taken at the same ambient temperature to minimise precision errors. Use of devices with a water-bath heated to a uniform temperature may reduce the significance of this problem[443].

QUS and osteoporosis

A number of large prospective and cross-sectional studies of older women have demonstrated that QUS can predict risk of fracture as well as DEXA and other established techniques[205, 425, 431, 444-466]. Recently, calcaneal QUS was shown to discriminate between patients with fractures at the wrist and other sites as well as axial DEXA.[467] Therefore, QUS could be used to identify those at risk of fracture and so increase the availability of bone densitometry services.

A recent large prospective study[466] of QUS and fracture in Swiss women found that low calcaneal QUS is associated with an increased risk of hip fracture. After a mean follow up of 2.5 years, 62 hip fractures amongst 7494 women were documented. After adjustment for age, the relative risk of fracture per SD reduction in QUS was 2.0 for the Achilles machine and 2.4 for the Sahara machine. Further adjustments for weight and clinical centre had little effect. Even more recently, a large prospective study was completed in the United Kingdom that demonstrated that QUS could predict fracture in *men* and women[452]. This study was of particular importance as the majority of clinical studies using QUS have only been undertaken in postmenopausal women.

Although QUS measurements do reflect bone mass[430], some studies suggest that QUS also assesses elements of bone quality, including trabecular thickness and connectivity[468, 469]. A recent prospective study[470] even demonstrated that low QUS values are associated with an increased risk of mortality and this persisted after adjustment for other factors associated with increased mortality such as age, weight, strength and existing medical conditions.

Population screening for osteoporosis

Although many studies have been published about osteoporosis in postmenopausal women, no trials have evaluated the effectiveness of screening; therefore no direct evidence that screening improves outcomes is available[471]. Support for population screening is based on the evidence that the prevalence of osteoporosis and fractures increases with age, that the short-term risk of fracture can be estimated by bone density tests and risk factors, and that the fracture risk among women with low bone density can

be significantly reduced with treatment. Black *et al*[472] concluded that there is ample justification for screening and treating elderly women.

Currently, screening unselected populations for osteoporosis is not recommended[209]. However, screening women over 65 years routinely and women aged 60-64 years with an increased risk has been recommended by the United States Preventive Services Task Force[473]. Similarly, the Canadian Clinical Practice Guidelines for the diagnosis and management of osteoporosis also recommend routine screening of women over 65 years[252]. The American College of Obstetricians and Gynaecologists Committee on Gynaecologic Practice has also recently recommended BMD testing in postmenopausal women over 65 years and postmenopausal women who present with fractures[474]. When considering screening programmes certain criteria must be met as shown in Box 4.

Box 4 Criteria for community screening programmes[475]

1. The disease has to be an important social problem
2. The test needs to be simple and safe, acceptable to the population and effective
3. There has to be an accepted and effective treatment
4. There have to be accepted standards on who to treat.
5. The programme for screening needs to be cost effective and there needs to be facilities for diagnosis and treatment

There is no doubt osteoporosis is a major problem, with 1 in 2 women and 1 in 3 men likely to sustain an osteoporotic fracture after 60 years of age in Australia[209]. Screening with QUS is simple and safe, and effective treatments exist, however,

monitoring of therapy cannot be currently conducted with QUS. In addition, there is no WHO criterion on treatment thresholds and this needs to be developed for QUS. Finally, QUS screening requires further study to examine cost-effectiveness[475].

Guidelines for use of QUS

There are few guidelines on how to use QUS, and the exact position of QUS in clinical practice has yet to be firmly clarified. Certainly experts agree that in the present form QUS cannot be used to diagnose osteoporosis for the reason that the WHO definition of osteoporosis is not applicable to QUS. Some possible approaches to the use of QUS in the management of osteoporosis have been reported by Gluer and Hans[455]. These include:

- QUS to estimate BMD;
- QUS as a stand alone approach;
- QUS as a pre-screening tool; or
- A composite approach in association in association with bone markers, clinical fracture risk and other diagnostic evaluations.

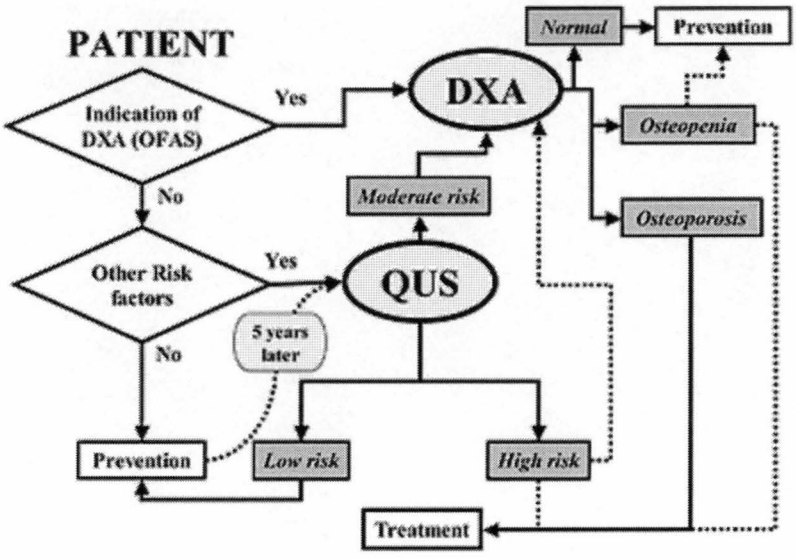
In the 2002 Canadian Clinical Practice Guidelines for the diagnosis and treatment of osteoporosis, it is stated that QUS appears to be effective in estimating risk of fracture in postmenopausal women over 65 years of age[252]. However QUS is not sufficiently precise for follow-up at clinically relevant intervals. The National Osteoporosis Society from the United Kingdom published a position statement in 2001 for the use of quantitative ultrasound in the management of osteoporosis[443]. The key recommendations are shown in Table 30.

Table 30 United Kingdom's National Osteoporosis Society Position Statement for use of quantitative ultrasound in the management of osteoporosis[443]

1.	QUS does not measure bone mineral content or density directly, it cannot be used to diagnose osteoporosis as currently defined by bone mineral content or BMD assessment.
2.	Low QUS is an independent risk factor for future osteoporotic fracture in postmenopausal women.
3.	Low QUS parameters are stronger predictors of low bone mass than clinical risk factors; individuals found to have low QUS parameters may either be referred for confirmation of the diagnosis by axial (preferably hip) BMD measurement or be advised to receive preventive therapy if other strong clinical risk factors are present.
4.	In most cases QUS measurements cannot be used to monitor bone loss or assess response to therapy in an individual patient.
5.	At present, the use of QUS for assessment of bone mass in children, pre-menopausal women, and men for clinical care purposes is not recommended.
6.	Trained staff must operate all QUS devices and they should be able to demonstrate precision of measurement within the manufactures specification. An experienced physician with specific knowledge of osteoporosis and its management must interpret results.

QUS and its assessed parameters, BUA, SOS or derived indices, can be used for assessing the risk of osteoporotic fractures (a) in the community in postmenopausal women, (b) as an improved method for targeting women for central BMD measurements to diagnose osteoporosis and (c) with care, to target antiresorptive treatments when low QUS measurements are present in addition to major clinical risk factors[443]. Hans *et al*[437] recently proposed guidelines for use of QUS in Switzerland taking into account the DEXA, QUS, and risk factors recognised in Switzerland (Figure 28). In their guidelines, a QUI T-score less than –1 and greater than –2.2 was considered low and high risk, respectively, when using the Sahara machine.

Figure 28 Proposed Swiss recommendations in management of osteoporosis which incorporates QUS with DEXA testing[437]



Interpretation of QUS T-scores

The original WHO decision to use a BMD T-score of –2.5 as a diagnostic threshold for osteoporosis does not apply to QUS[438, 476, 477]. Several recommendations have been published in recent years. Baran *et al*[478] recommended that if a T-score lies between –2 and 1 for women under 65 years or between –2 and 0 for women over 65 years than further investigation should be performed by DEXA at the spine and hip to exclude a false negative. The United Kingdom National Osteoporosis Society recommended that if a patient has a low QUS measurement then referral for DEXA assessment is warranted[443]. Miller *et al*[257] proposed that if an individual has a peripheral bone mass T-score less than –1, they would not need additional central measurements with DEXA.

Frost *et al*[438] found using three different QUS devices, that the WHO criteria for the diagnosis of osteoporosis in postmenopausal women cannot be applied to calcaneal QUS measurements and that different QUS devices have different optimum T-score thresholds for diagnosing osteoporosis. However, the authors found that an estimated BMD T-score threshold of –1.8 may be appropriate for identifying postmenopausal women at risk of osteoporosis using ultrasound attenuation and velocity measurements at the calcaneus. The study used one device that was used in the current research (Sahara). It is acknowledged there is a lack of comparability in using a set T-score across all sites and devices, although these discordances do not affect the power of QUS measurements to calculate fracture risk[431]. Frost *et al*[438] proposed revised criteria for QUS that have been shown to be applicable to Sahara device (Table 31). In a recent study using the revised QUS criteria, Frost *et al*[479] found similar proportions of postmenopausal women identified as osteopaenic or osteoporotic as with BMD.

Table 31 Suggested interpretation of QUS estimated heel BMD T-score by Frost *et al*[438, 479]

	Estimated heel BMD T-score
Normal	≥ -0.5
Osteopaenia	< -0.5 but >-1.8
Osteoporosis	≤ -1.8

Pharmacy, point of care testing, education and osteoporosis

Community pharmacies are increasingly providing services other than traditional dispensing of medications. For example, there have been studies demonstrating successful interventions to control blood pressure[71-75], diabetes[76], and cholesterol [76, 77]. Furthermore, efforts in community pharmacies have demonstrated patients can benefit from a pharmacy-conducted smoking cessation clinic[78], and weight reduction clinic[79]. Pharmacists (in the United States) are also providing some vaccinations [80, 81].

Osteoporosis is of increasing concern and in the absence of interventions, the prevalence of osteoporosis-related conditions is predicted to increase over the next two decades from 10% to 13% of the population in 2021[183]. Lack of time and limited access to bone density testing have been cited as key barriers that limit doctors' ability to detect early bone loss[480]. It therefore appears reasonable that if technology is available and is portable, then community pharmacies may be an ideal place to screen "high-risk" individuals, such as elderly women. This is of particular benefit to rural residents as they are less likely than urban residents to obtain preventive health services in general[423]. Furthermore, rural populations generally have lower incomes, less education, and have longer travel times to their usual source of medical care than urban populations[423]. Rural populations are less likely to have access to diagnostic equipment (e.g., DEXA) for osteoporosis than urban populations[481].

Osteoporosis screening by pharmacists is feasible owing to their accessible and stable community presence, free exposure to people, and collaborative relationships with doctors[427]. There has been some evidence of community pharmacists performing osteoporosis screening[426]. Furthermore, pharmacists can play a key role in promoting

adherence to pharmaceutical osteoporosis therapy, for which adherence is often poor[482, 483]. Additionally, with their expertise regarding non-prescription products, pharmacists can encourage the use of calcium when warranted[428], considering they often feature as a preferred source of drug information[484].

Although peripheral bone density measurement devices have been used at pharmacies and other venues, there are very few published reports worldwide on programmes involving their use[426, 428]. It has only been recently reported that QUS can predict fractures in men as well as women[452] and thus further guidelines are required before screening men with QUS can be advocated.

Elliott *et al*[481] evaluated elderly women's knowledge of their skeletal status, assess adequacy of calcium intake, determined the prevalence of low bone density, and determined whether peripheral bone density testing led to medical interventions in a group of rural, elderly women recruited in 5 community pharmacies in the United States. Of 133 women, 20% had calcaneal osteoporosis, defined as a T-score $\leq$ -2.5 (calcaneal bone density). Thirty percent of women met National Osteoporosis Foundation (NOF) treatment criteria based on heel bone density and NOF-designated risk factors. Of those meeting treatment criteria, 75% were unaware of their low bone mass. Half of the women received the recommended calcium intake. Women who had discussed bone density test results with their physicians were more likely to receive central DEXA measurements and/or start antiresorptive therapy than women who did not. It was found that community screening of rural, elderly women by peripheral bone density measurement can lead to medical interventions in such individuals[481]. The authors concluded in a subsequent publication that the community pharmacy-based osteoporosis screening programme was well accepted by physicians[426].

Another study assessed the monetary value placed on, pharmacy-based bone density screening. In addition, the study evaluated doctors' response to peripheral bone mass measurements. A total of 197 women over 50 years of age in four rural US community pharmacies completed a questionnaire and underwent calcaneal bone density testing. The results were sent to participants' primary care providers. Women were willing to pay a median of US$25 for the screening. Of 18 responding clinicians with patients in this study, 72% found the results useful. Of the 67 responding doctors, 51% supported pharmacy-based bone mass measurement. Doctors receiving such results found them useful and indicated a willingness to use them in decision-making[485].

Aims of study

The aim of this project was to assess the suitability of community pharmacies as osteoporosis screening centres for high-risk patients living in rural communities with limited access to bone density measurements - through a full evaluation of the feasibility, outcomes and acceptability (to doctors and the public) of such a programme in Australia. The specific hypothesis to be tested was that subjects found to be at risk of osteoporosis on testing in a community setting would seek medical advice. It was anticipated that data can be collected demonstrating pharmacists can fulfil an important role in the prevention of osteoporosis by detecting, educating and referring patients at risk of the disease.

Chapter 2: Methods

Training to use Sahara clinical bone sonometer

Under the supervision of Associate Professor Graeme Jones and an experienced technician, the pharmacist (MN) underwent extensive preliminary training to use the Sahara Clinical Bone Sonometer. This included an introductory video and manual that provided an overview of the Sahara's key features, principles of operation and assessment of fracture risk. The portable instrument was provided at no expense to the research team by Roche Diagnostics, (Castle Hill, Australia). The manufacturer, Hologic, Waltham, MA, provided reference population data for Australian women. The machine was fully serviced and calibrated prior to testing by a certified company.

The proposed Frost[438] classification for QUS and osteoporosis was validated prior to the commencement of the screening by the research pharmacist (MN) who conducted the screening. Paired tests were performed using the QUS device on the non-dominant side (the two tests were then averaged) of 26 volunteer postmenopausal women presenting to a research institute for osteoporosis assessment (Menzies Centre for Population and Health Research). All patients had dual energy x-ray absorptiometry at the lumbar spine, and right femoral neck (Hologic QDR2000 densitometer, Waltham, MA). The precision of the pharmacist performing the validation and screening was also measured.

Screening sites

The project was conducted at 6 rural sites (as defined by The Pharmacy Access/Remoteness Index of Australia {PhARIA} classification) in Tasmania, Australia

to assess the feasibility of establishing community pharmacy-based osteoporosis screening programmes. The pharmacies were selected from a range of rural areas in Tasmania possessing a private location within the pharmacy to perform the screening for 2-3 weeks. The selected pharmacies (all possessing a PhARIA of ≥ 2) were identified from previous research or were teaching sites and affiliated with the University of Tasmania. Tasmania has a population of approximately 473,000 with approximately 65,000 over 65 years as of 2001[486]. Elderly individuals over 65 years were screened and, if appropriate, referred to their GP for follow-up testing and management. Local GPs and Divisions of General Practice were fully informed of the project in advance where possible through telephone, newsletters and practice meetings.

The research pharmacist performed osteoporosis risk screening for 2-3 weeks in each of the 6 community pharmacies over a 6-month period (March-August 2003).

Recruitment

Each screening site was contacted approximately one month prior to the screening and visited to inform staff of the project. The pharmacists were strongly encouraged to involve all pharmacy assistants, as they would recruit the majority of the patients entering the study. The pharmacies were provided with a poster (7) to place in a prominent area of the pharmacy to inform public of the screening. In addition, local newspapers published an editorial on the screening (8, 9) and advertisements were placed in the local papers (where possible) and fliers were placed on counters in the pharmacy. Local physiotherapists were informed and asked to refer women over 65 years where possible. The recruitment of patients commenced 2 weeks prior to the screening. Patients were provided with a reminder card for their appointment and all

patients recruited were screened (by pharmacy staff) for possible contraindications to the screening (see exclusion criteria). Furthermore, patients phone numbers were recorded for the pharmacist performing the screening to contact participants prior to their appointment as a reminder, and further screen for patients that may not be suitable for the test (e.g. < 65 years, on bisphosphonates, raloxifene). Each pharmacy was given an appointment diary; with each appointment scheduled for approximately 45-60 minutes between the hours of 9am and 5pm. Hence, approximately 35 women could potentially be screened per week.

Participants and risk factor questionnaire

After obtaining informed consent, each individual was questioned about their awareness of factors that constitute risks for osteoporosis, using a modified but previously validated knowledge questionnaire[487] (Table 32; true or false answers). Statements not attempted were automatically treated as incorrect. The subject's height and weight was measured and their body mass index calculated [BMI = weight (kg)/height^2 (m)]. The research pharmacist then assessed each person's risk factors for osteoporosis (e.g., current corticosteroid use, BMI < 18 kg/m^2, previous fragile fracture after the age of 50 years). Variables recorded for each person included demographic information, weight, height, smoking/alcohol, medical history (e.g., previous fracture), and medication history. Subjects were also questioned about previous HRT use, number of pregnancies, marital status and highest education level reached.

During the initial risk screening patients were asked a series of questions to elicit their calcium intake. The food frequency questionnaire had been previously validated in

Caucasian Australian women against 4 day weighed dietary records. The correlation between methods for estimated calcium intake was high ($r = 0.79$, $p = 0.001$)[488].

Reported sun exposure was scored from 0 (minimum) to 7 (maximum) as suggested by Bruce *et al*[489] This was derived from three sub-scores: frequency of going outdoors, ranging from never (0) to most days (3); avoidance of direct sunlight, ranging from always (0) to never (2) and having acquired a suntan in the previous 6 months, ranging from nil (0) to an obvious tan (2). Inderjeeth *et al*[490] had also previously validated this as a measure to assess vitamin D deficiency in older non-institutionalised southern Tasmanians.

Table 32 Modified knowledge questionnaire used to assess subjects' awareness of osteoporosis risk factors[491]

Q1. One in two women and one in three men over 60 will develop an osteoporotic fracture
Q2. A family history of osteoporosis is not a risk factor for osteoporosis
Q3. An early menopause, such as after a hysterectomy, is not a risk factor for osteoporosis.
Q4. A lifetime low intake of calcium will increase the risk of osteoporosis
Q5. Smoking is not a risk factor for osteoporosis
Q6. Thin women are more often affected by osteoporosis than heavy women
Q7. Weight bearing exercise such as walking can help prevent osteoporosis
Q8. After age 40, it is too late for people to increase their calcium intake to prevent osteoporosis
Q9. After menopause, osteoporosis may be slowed down by taking oestrogen
Q10. All individuals lose bone mass after 40 years of age
Q11. Normally bone loss slows down after menopause
Q12. A diet high in calcium throughout life can help prevent osteoporosis
Q13. Postmenopausal women need about 1000-1500mg of calcium each day
Q14. Dairy products are a major source of calcium
Q15. It is normal for bone loss to continue throughout life
Q16. Active women are at higher risk for osteoporosis than inactive women
Q17. Alcohol abuse is not linked to the incidence of osteoporosis

Exclusion criteria

The following reasons constituted study exclusion:

- currently diagnosed with osteoporosis;
- currently treated with bisphosphonates, raloxifene, calcitriol, or calcitonin;
- less than 65 years;
- known DEXA scan within previous two years; or
- anatomical abnormality of the foot to be tested that would interfere with a calcaneal bone ultrasound, including moderate to severe oedema.

Self-report fracture definition

Subjects were considered to have a history of a fragility fracture only if the fracture had occurred after the age of 50 years and resulted from a fall from standing height or lower, or minor trauma. A fracture was excluded if it was caused by severe trauma (traffic accidents, impact of moving objects, and falls from greater than floor height), as was fracture of the skull, face, and metacarpals and phalanges.

Calcaneus measurement

QUS measurements were taken at the non-dominant calcaneus (in accordance with manufacturer's recommendation). BMD measurements were expressed as T- and Z-scores based on the mean and SD of the manufacturer's reference population.

The pharmacist reviewed the printout of the bone density test with the subject, and explained how her BMD test result compared with reference population data. The subject's dominant side was only tested if they had broken skin or the subject reported

previous broken bones on the non-dominant calcaneus or if there was difficulty positioning the non-dominant foot (e.g., bunions). The individual was asked to see her GP for further assessment and/or treatment - subjects with an estimated BMD T-score ≤ - 1.0 as used in a previous study[492] was considered sufficient to warrant further investigation in a subject. Subjects who were unable to be positioned correctly were referred to their GP for further evaluation. A 5-year fracture risk was calculated and the usual 5-year fracture risk for that women's particular age group was also calculated – see below. Likewise, subjects who had T-scores > -1, but had strong risk factors such as previous fragility fracture, current corticosteroid use or parent fractured a hip, were also referred to their GP for further evaluation. The pharmacist sent GPs a copy of the results (Figure 29 and Figure 30) with an explanation, along with any risk factors identified (e.g., a previous fragility fracture or current corticosteroid use).

Tested subjects were provided with written educational material from Osteoporosis Australia (11) and verbal counselling about osteoporosis risk factors, diet and the importance of regular physical activity. A refrigerator magnet (used in a previous project[493]) was given to subjects with a low calcium intake (<1500 mg/day or <1000 mg/day if treated with HRT) to remind them of the importance of maintaining an adequate calcium intake. A calcium counter[270] was also provided to subjects to inform them of the calcium content in various foods.

Table 33 Usual 5-year fracture risk (Tasmanian Data)[221]

Age	Male	Female
50-54	3.9	3.1
55-59	3.4	5.0
60-64	4.1	6.1
65-69	5.5	7.0
70-74	6.3	9.1
75-79	9.5	14.9
80-84	12.4	20.0
85+	21.5	35.9

Formula for calculation of:

$$\text{5 year fracture risk} = \text{Age group risk (\%)} \times 1.5^{-z}$$

N.b., 1.5 is the odds ratio for sustaining any fracture with 1 SD decrease in BUA[214] and z is the patient's BUA compared to an aged-matched subject. Associate Professor Graeme Jones supplied the formula. Women over the age of 85 years (n = 9) were unable to have a 5-year fracture risk assessment due to the manufacture of the QUS device not having reference data to calculate a Z-score.

The ultrasound machine was subject to daily quality control (QC) checks, using a phantom provided by the manufacturer. Patient measurements did not proceed until the phantom QC was successful (Figure 31).

Figure 29 Example of letter sent to subject's usual GP along with report generated by the Sahara ultrasound device

DATE 18/08/2003

Dear Dr XXXXX

RE: YOUR PATIENT: XXXX XXXXX

The Faculty of Health Science at the University of Tasmania is conducting a project to assist in the detection of patients who are at risk of osteoporosis, using a heel ultrasound machine that has been validated to predict risk of sustaining an osteoporotic fracture.

There is no doubt that osteoporosis is a major health issue. It is estimated that 1 in 2 women and 1 in 4 men over the age of 60 years will suffer from an osteoporotic fracture in Australia. The US Preventive Task Force has suggested that all women aged over 65 years should be screened for osteoporosis[1], and this forms the basis of this study.

On 18/08/2003 XXXX presented to the Sorrel Chemmart Pharmacy and, after providing informed consent, had her heel bone density measured by the Sahara Bone ultrasound.

The Scientific Advisory Council of the Osteoporosis Society of Canada[2] have stated that Calcaneal quantitative ultrasonometry appears to be effective in estimating risk of fracture in post-menopausal women over the age of 65 years. XXXXX's complete heel ultrasound results are attached to this letter. Based on this result we have also calculated a 5-year risk for fracture.

Her estimated heel T-Score was: -2.2

Her predicted 5-year risk for suffering an osteoporotic fracture is: 36.2% *

This result is *not* capable of diagnosing osteoporosis but is a measure for assessing the patient tested for risk of osteoporosis. A table is provided to assist you with the interpretation of the heel ultrasound result.[3]

We suggest that patients with a T score <-1.0 are at an increase risk for osteoporosis and may need further investigation. Your patient's T-score of **-2.2** indicates that if a central DXA test is performed they are likely to be **osteoporotic** (see table shown overleaf).

We hope this test result can assist you in the management of your patient. We also provided a copy of the result to your patient to discuss with you on their next scheduled appointment, along with some educational material from Osteoporosis Australia.

Yours sincerely

Mark Naunton	Gregory Peterson	Graeme Jones
Project Pharmacist/PhD student	**Professor of Pharmacy**	**Associate Professor**
TASMANIAN SCHOOL OF PHARMACY	TASMANIAN SCHOOL OF PHARMACY	MENZIES CENTRE/RHEUMATOLOGIST

1 Nelson, HD et al Annals of Internal Medicine, 2002. 137(6): 529-41.
2 Brown JP, Josse RJ, for the Scientific Advisory Council, Osteoporosis Society of Canada. *CMAJ* 2002;167(10 Suppl) S1-S34.
3 Frost, ML et a. Osteoporos Int, 2000.11: 321-330

* Usual 5-year fracture risk for an 80-84 year old female = 20%.

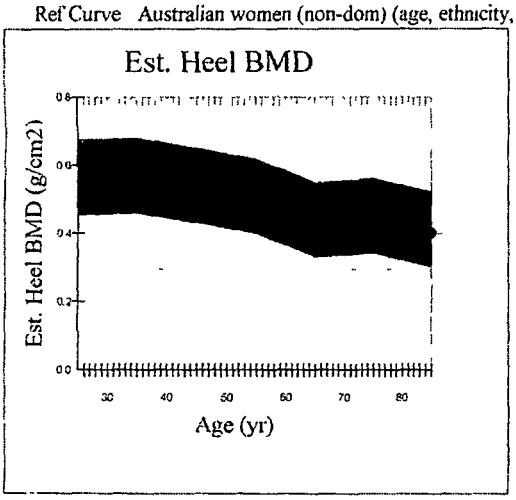
Figure 30 Example of report generated by the Sahara ultrasound device and sent to the subject's usual GP along with the covering letter

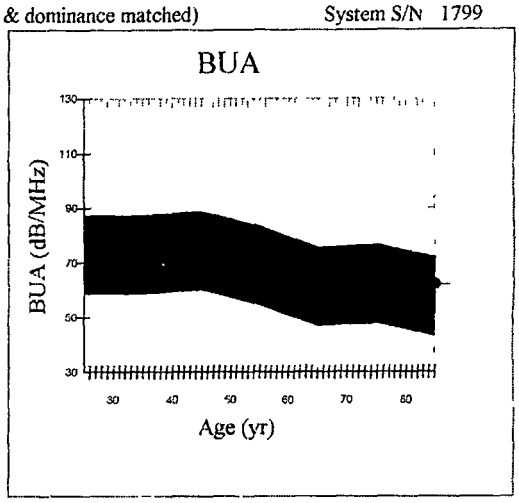
Name DAPHNE [redacted]	Sex Female	Report Date 11-02-2004
ID#1 daphne	Study v2	
DOB 09-03-1918	Menopause Age 42	Age 85
Height 155.0 cm	Weight 66.0 kg	Operator
Ethnic White	Dominance. Left	Referring Physician [redacted]
Comments		

Est BMD 0 400 g/cm2 QUI/Stiffness 75 3 BUA 62 0 dB/MHz SOS 1514 4 m/s

Exam Date 26-03-2003 12 15 Foot Measured Right

Ref Curve Australian women (non-dom) (age, ethnicity, sex, & dominance matched) System S/N 1799





Est BMD: 0.400		
% of young normal (35) 70%	T-score -1 5	
% of age matched. 97%	Z-score -0 1	

BUA 62 0		
% of young normal (45) 83%	T-score -0 9	
% of age matched 107% *	Z-score 0 3	

Exam Observation

* Used to Calculate 5-year fracture risk

HOLOGIC

SAHARA CLINICAL BONE SONOMETER™

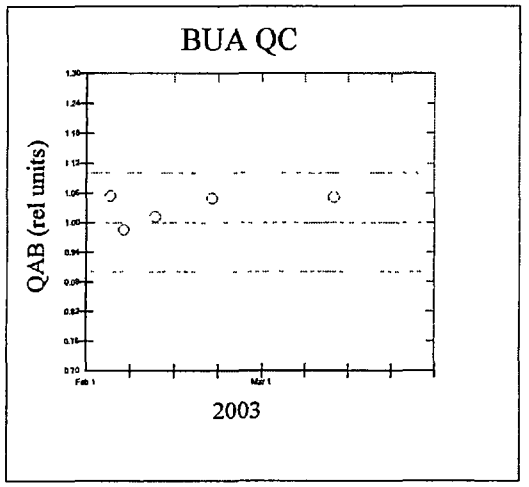
Figure 31 An example of a QC report – if successful the Sahara device will display "QC Successful" on the portable laptop computer and ultrasound device

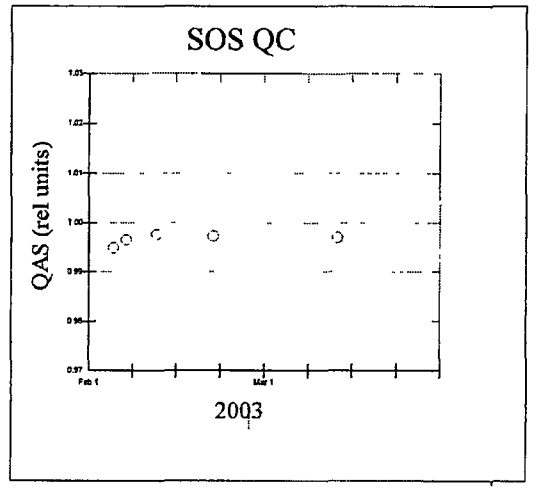
Phantom. ref-1799 - 1799 Report Date: 13-03-2003

Labeled BUA: 31.0

Labeled SOS: 1534.7

System S/N: 1799





Reference Values	Plot Statistics
limits = 0.100	n = 5
mean = 1 0	mean = 1.0305
	SD = 0.0305

Reference Values	Plot Statistics
limits = 0 010	n = 5
mean = 1.0	mean = 0 99663
	SD = 0 00109

Patient follow-up

Subjects were followed-up by phone approximately twelve weeks post-screening and were sent a postal survey. Approximately 4 days after the surveys were mailed, subjects were telephoned (by MN, who performed the screening) to ensure the surveys had arrived and to determine the outcome, if any, of the initial screening process (e.g., re-testing by GP, dietary or drug treatment commenced, self-care behaviours implemented, or medical advice sought). Patients were not asked their opinion of the service as this was assessed in the postal survey.

The postal survey was also designed to assess outcomes, if any, of the initial screening process (e.g., re-testing by GP, dietary or drug treatment commenced, self-care behaviours implemented or medical advice sought) and compare responses to the telephone survey to ensure validity of the telephone survey. At follow-up, each individual was again questioned about their awareness of factors that constitute as risks for osteoporosis and to assess whether there had been an improvement in knowledge. All subjects were asked to provide an estimate of the cost they would be willing to pay to have this screening procedure performed in practice. In addition, subjects were asked to rate the service they received and also whether they thought their GP was satisfied with the screening procedure being performed.

All GPs and pharmacists exposed to the screening were sent a satisfaction survey to assess their opinion of the screening (12, 13).

Cost benefit analysis

A cost benefit analysis was performed using data from the 2001 Access Economics Report - The Burden of Brittle Bones: Costing Osteoporosis in Australia[183]. Population statistics was also obtained for 2001 from the Australian Bureau of Statistics[494]. In addition, relevant costing information for osteoporotic fractures in women greater than 65 years was obtained from Dr Kerrie Saunders (University of Melbourne, Department of Medicine).

Statistical analysis

Continuous variables were described with median and range, and categorical variables as frequency and percentage. Chi-square analysis was used to test for significance of difference between proportions. Non-parametric techniques were principally used to describe patient characteristics and examine differences in variables between sub-groups of patients. Kappa statistics were employed to assess the agreement between DEXA BMD T-score values and estimated BMD T-score in the pre-screening sample.

A p value less than 0.05 were considered statistically significant. The statistical analysis was performed using Statview® 5.01 (Abacus Concepts Inc., Berkeley, CA, United States).

Ethics approval

The Royal Hobart Hospital Research Advisory Committee and the Southern Tasmania Health & Medical Human Research Ethics Committee approved the project. All subjects gave written informed consent.

Chapter 3: Results

1: Validation of the Frost classification for osteoporosis using QUS

A total of 26 postmenopausal women consented to QUS testing in an academic institution that provided additional central DEXA scans for patients referred by their GP for osteoporosis screening/diagnosis. The 26 subjects provided two tests (the two tests were then averaged) from their non-dominant heel, for assessment of the Frost[438] classification for quantitative heel ultrasound in addition to DEXA assessment at the femoral neck and lumbar spine (Table 34). Table 35 shows operator precision prior to osteoporosis screening in community pharmacies. The mean coefficient of variation for QUS on the 26 patients was 2.6% (range 0.5% - 8.2%).

Table 36 categorises patients as normal, osteopaenic, and osteoporotic on QUS and DEXA, and Table 37 provides agreement between the QUS and DEXA. Table 38 demonstrates that the revised classification (by Frost) when QUS is applied is both sensitive and specific for osteoporosis. Graph 1 and 2 demonstrate a positive correlation between QUS measurements at the calcaneus and DEXA measurements conducted at the femoral and lumbar spine.

Table 34 QUS and femoral neck/lumbar spine DEXA T-scores for 26 postmenopausal women volunteers prior to screening

Subject	DEXA T-score		QUS T-score	
	Lumbar spine	Femoral neck	Test 1	Test 2
1	-3.4	-1.7	-2.2	-2.1
2	0.4	1.5	1.2	1.1
3	-0.5	-2.2	-1.7	-1.0
4	-1.0	0.7	1.1	1.0
5	-2.5	-1.6	-2.9	-2.7
6	-2.7	-3.3	-3.3	-3.2
7	1.9	0.8	1.0	1.0
8	-1.9	-1.4	-0.9	-0.7
9	-2.8	-1.8	-2.1	-1.9
10	-1.0	-0.7	-1.8	-1.6
11	-1.1	-0.2	-0.6	-0.6
12	-3.9	-2.2	-2.9	-2.7
13	1.9	0.8	1.0	1.0
14	0.5	0.7	0.5	0.4
15	-1.6	-2.0	-1.2	-1.4
16	2.0	-0.1	0.0	0.1
17	0.3	-0.1	0.8	0.7
18	-1.5	-1.5	-1.3	-1.2
19	-0.2	-0.2	-0.5	-0.5
20	-1.8	-2.7	-2.6	-2.5
21	0.4	0.2	-0.1	-0.2
22	-2.3	-2.2	-2.3	-2.3
23	-1.8	-0.9	-1.2	-1.1
24	-1.6	-1.2	-0.8	-0.8
25	1.9	-0.5	0.4	0.6
26	-1.6	0	-1.3	-1.2

Table 35 QUS estimated heel BMD (g/cm^2) for 26 postmenopausal women volunteers

Subject	QUS estimated BMD		Coefficient of Variation
	Test 1	Test 2	
1	0.339	0.350	0.023
2	0.704	0.690	0.014
3	0.382	0.417	0.062
4	0.687	0.680	0.007
5	0.249	0.273	0.065
6	0.211	0.217	0.020
7	0.688	0.683	0.005
8	0.479	0.501	0.032
9	0.268	0.301	0.082
10	0.378	0.406	0.069
11	0.503	0.499	0.006
12	0.246	0.271	0.068
13	0.688	0.685	0.003
14	0.627	0.615	0.014
15	0.441	0.406	0.058
16	0.583	0.587	0.005
17	0.658	0.650	0.009
18	0.430	0.436	0.010
19	0.510	0.517	0.010
20	0.287	0.298	0.027
21	0.567	0.560	0.009
22	0.323	0.318	0.011
23	0.443	0.453	0.016
24	0.480	0.485	0.007
25	0.619	0.644	0.028
26	0.423	0.430	0.012
Mean Coefficient of Variation; % (range)			2.58 (0.5 - 8.2)

Table 36 Classification of 26 postmenopausal women volunteers for osteoporosis using DEXA and heel QUS.

Calcaneus QUS	DEXA at spine or femoral neck			Total
	Normal	Osteopaenia	Osteoporosis	
Normal	10	0	0	10
Osteopaenia	1	8	0	9
Osteoporosis	0	1	6	7
Total	11	9	6	26

Table 37 Agreement between QUS and DEXA for classification of osteoporosis, osteopaenia, and normal

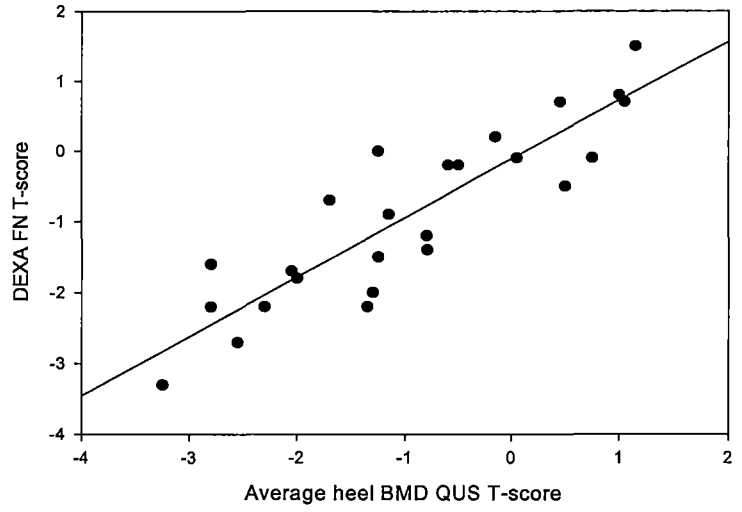
	Kappa values
Osteoporosis	0.90
Osteopaenia	0.83
Normal	0.93

All $p<0.001$

Table 38 Sensitivity and specificity of QUS for classifying women with osteoporosis /osteopaenia or normal results on DEXA

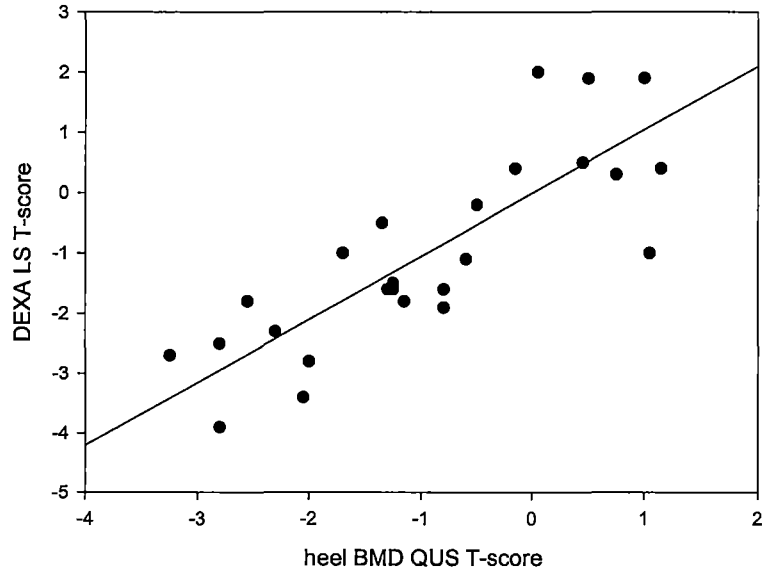
QUS scan	DEXA Normal	DEXA osteoporosis/osteopaenia	Total
Normal	10	0	10
Osteoporosis/osteopaenia	1	15	16
Total	11	15	26
Sensitivity: 15/15 = 100% Specificity: 10/11 = 91%			

Graph 1 Correlation between DEXA femoral neck (FN) T-score and QUS heel BMD T-score



r^2 FN = 0.8, y = -0.11 + 0.836x

Graph 2 Correlation between DEXA lumbar spine (LS) T-score and QUS estimated heel BMD T-score



r^2LS = 0.7, y = 0.05 + 1.05x

2: Osteoporosis screening in community pharmacies

A total of 408 subjects were referred to the pharmacist at the 6 rural sites, which were a median of 45 km (range 25-110 km) from a central DEXA unit for osteoporosis testing. Sixty-three subjects were excluded from screening because of known DEXA testing (n=12), current osteoporosis treatment other than simple vitamin D/calcium/HRT (n = 16), anatomical abnormality (n= 8) or age less than 65 years (n=27). Table 39 displays the number of subjects screened at each site (following exclusions). Figure 32 shows a flow chart of subjects presenting to the pharmacist for screening. Table 40 summarises the clinical and demographic features of the 345 subjects who were screened.

Table 39 Number of subjects screened at each rural pharmacy

Site	Location	Number of subjects screened	Mean number of subjects screened per day
1	Southern Tasmania PhARIA classification: 3	38	5
2	North West Tasmania PhARIA classification: 4	47	5
3	Northern Tasmania PhARIA classification: 3	54	5
4	Southern Tasmania PhARIA classification: 3	78	6
5	Southern Tasmania PhARIA classification: 2	78	6
6	Southern Tasmania PhARIA classification: 2	50	6

Figure 32 Flow-chart of subject outcomes following osteoporosis screening

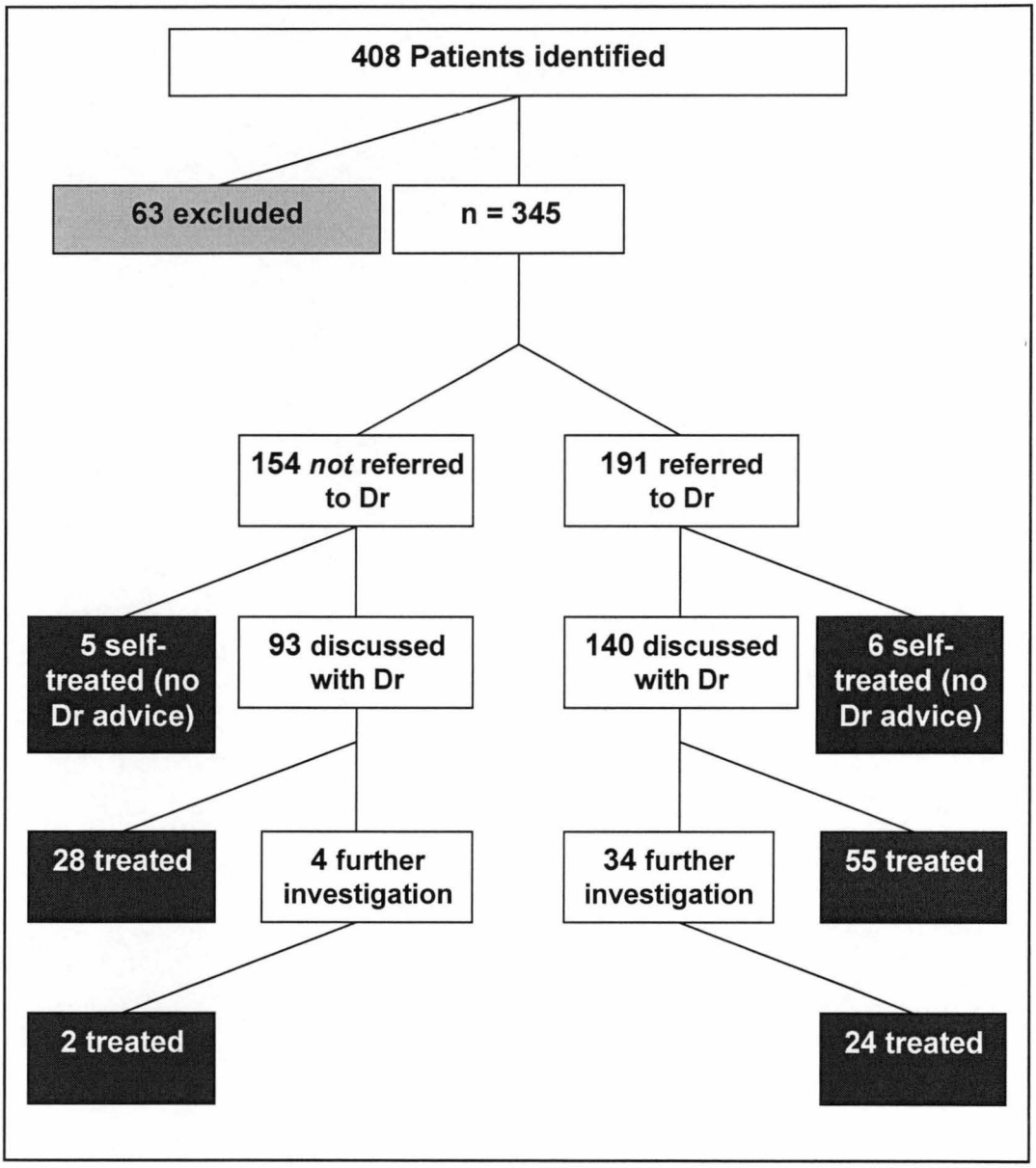


Table 40 Characteristics of subjects participating in the osteoporosis screening

	n = 345	
Age; years (median & range)	71	65-91
Smoking Status (%)		
current	23	(7)
never	234	(68)
ex < 10 years	25	(7)
ex > 10 years	63	(18)
Marital Status (%)		
married	171	(50)
widowed	138	(40)
divorced	26	(7)
de facto	2	(1)
single	8	(2)
Education (%)		
primary school	190	(55)
high school	107	(31)
technical qualification	36	(11)
university	8	(2)
no formal schooling	4	(1)
Body Mass Index (median & range, kg/m^2)	27.4	(15.9-47.1)
BMI > 30 (%)	105	(30)
BMI 25-30 (%)	124	(36)
Number of chronic medications (median & range)	4	(0-14)
none (%)	27	(8)
one, two or three (%)	142	(41)
four or five (%)	84	(24)
six or more (%)	92	(27)
Number of 'PRN' medications (median & range)	1	(0-6)
Number of complementary medications (median & range)	0	(0-13)
Current calcium supplements (%)	55	(16)
Current vitamin D supplements (%)	35	(10)
Current HRT (%)	42	(12)
Previous HRT use for > 1 year (%)	47	(16)
Medications that increase risk of osteoporosis (%)	93	(27)
oral corticosteroids	20	(6)
inhaled corticosteroids	26	(8)
thyroxine	35	(10)
valproate/carbamazepine/phenytoin	7	(2)
loop diuretics	23	(7)

Table 40 Continued....

Medications that increase risk of falls (%)	265	(77)
benzodiazepines	55	(16)
anti-cholinergics	41	(12)
anti-hypertensives	241	(70)
opiates	29	(8)
Self-reported risk factors for osteoporosis (%)	248	(72)
parent broke a hip	29	(8)
previous fracture > 50 years	68	(20)
menopause <45 years (natural or surgical)	108	(31)
current corticosteroid use	20	(6)
loss of height (> 1 inch or 2.5cm)	112	(32)
rheumatoid arthritis	30	(9)
current smoking	23	(7)
excessive alcohol (> 140 g/week)	2	(1)
Calcium intake (median & range, mg/day)	812	(69-3138)
0-499 mg (%)	58	17
500-999 mg (%)	166	48
1000-1499 mg (%)	81	23
≥1500 mg (%)	40	12
Knowledge Score (median & range, /17)	10	(1-17)
Score < 9 (%)	131	(38)
Sun score (median & range, /7)	5	(0-7)

Subjects' QUS characteristics and fracture risk

Table 41 provides the characteristics of estimated BMD T-scores and heel BUA Z-scores that were reported to subjects' GP. Figure 33 and Figure 34 display the distribution of subjects' estimated T-score and BUA Z-score, respectively. The median T-score was –0.8 (-3.0-1.9) and the median BUA Z-score was 0.7 (-2.1-4.2). This correlates to a median 5-year fracture risk of 6.9% (range: 1.5-38.9) for all women. The median 5-year fracture risk for subjects reporting a previous fracture was significantly higher (9%), compared to those not reporting a previous low trauma fracture (6.3%), (MW U = 6849, z = -2.9, p = 0.004). Figure 35 displays the age-related decline in estimated BMD T-score as assessed in the community pharmacy.

The majority of subjects (93%) had their non-dominant heel measured. There was no difference between the estimated BMD T-score in those who had their non-dominant heel tested (median = -0.8, range: -2.9-1.9) compared to those who had their dominant heel tested (median = -1.1, range: –3.0 – 1.8; MW U = 3684.5, z = -0.4, p = 0.7).

Table 41 Heel QUS indices and fracture risk that was reported to GPs.

	Median	Range
Estimated BMD (g/cm^2)	0.480	(0.241-0.780)
Estimated BMD T-score	**-0.8**	**(-3.0 – 1.9)**
T-score ≤ -1.8; ***likely osteoporosis*** *(%)*	69	(20)
T-score >-1.8 < -0.5; ***likely osteopaenia*** *(%)*	159	(46)
T-score ≥ -0.5; ***likely normal*** *(%)*	117	(34)
BUA (dB/MHz)	71.5	(30.9 - 122.4)
BUA Z score	0.7	(-2.1- 4.2)
BUA Z score < 0 (%)	92	(27)
BUA Z score < -1 (%)	25	(7)
5 –year fracture risk (%)	**6.9**	**(1.5-38.9)**
SOS (m/s)	1535.7	(1474.1- 1619.6)

Note: SOS = speed of sound, BUA = broadband ultrasound attenuation

Figure 33 Distribution of subjects' (n = 345) estimated BMD T-score

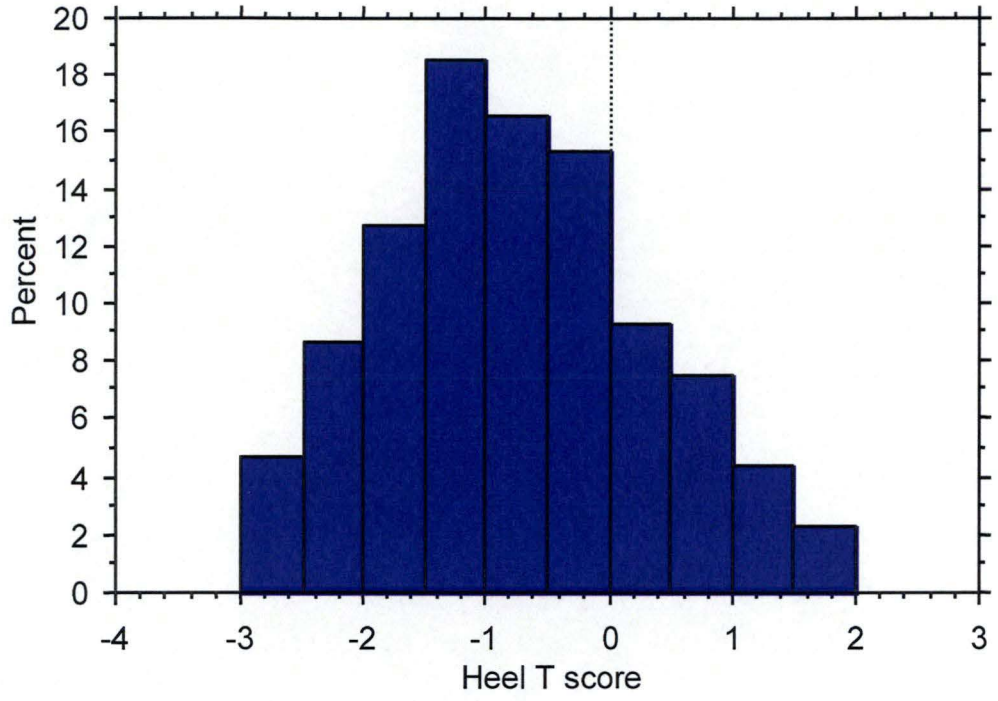


Figure 34 Distribution of subjects' (n = 336) BUA Z-score (< 0 indicates aged-matched increased risk for fracture)

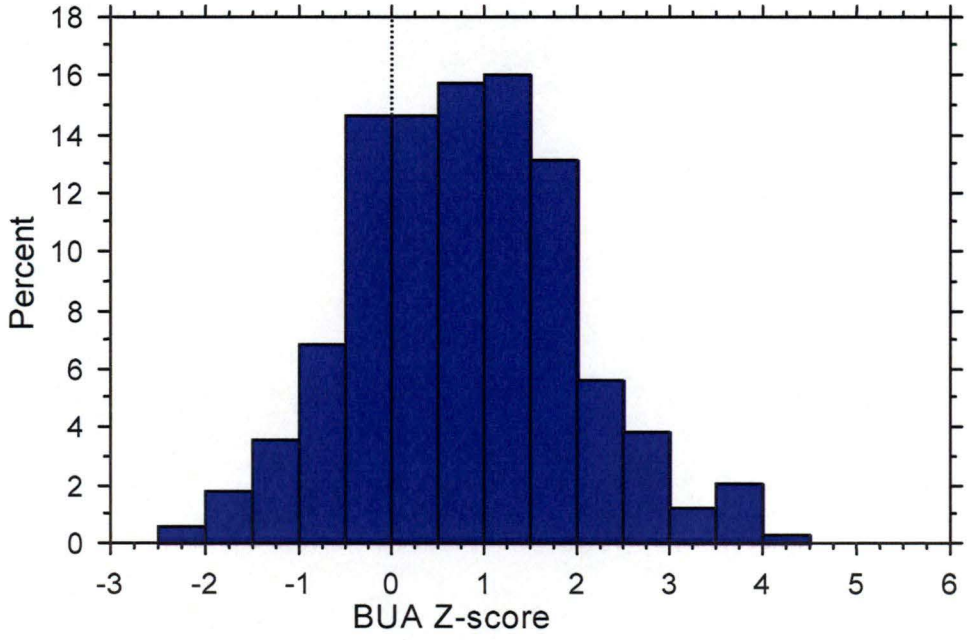
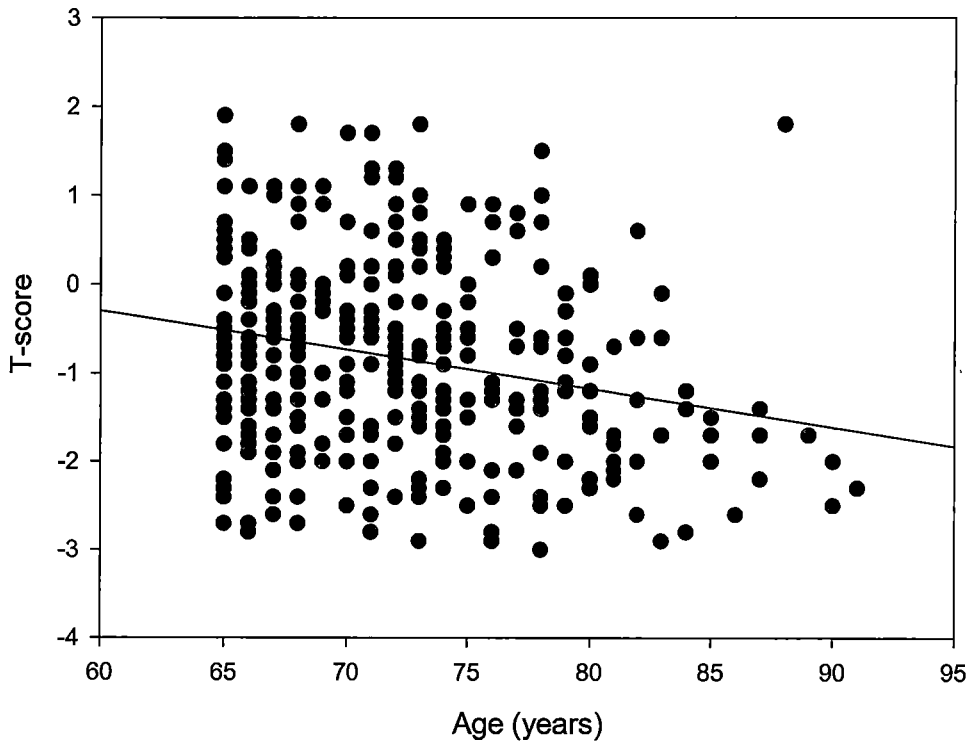


Figure 35 Age-related decline in estimated BMD T-scores

Y=2.338 – 0.044x, r2 = 0.056

Rho = -0.213, z = -3.95, p < 0.0001



Principal outcomes

Table 42 displays a summary of the principal outcomes following the screening in the community pharmacies. Follow-up data from the postal survey was available for 89% of subjects, and 100% of subjects were briefly interviewed by phone. Approximately two-thirds of subjects had discussed their results with their GP and 11% had undergone further investigation. At the time of follow-up, a further 4% were awaiting further investigation. One third (34%) of subjects reported commencing a medication following the screening and two-thirds had reportedly made lifestyle changes. Table 43 displays the median knowledge score of subjects before and after the screening, and Table 44 displays the percentage of correct responses to the various statements before and after the screening.

Table 42 Summary of principal outcomes following the osteoporosis screening.

	Phone Survey (n =345)		Postal Survey (n=308)	
Discussed results with GP (%)	233	(68)	194	(63)
Underwent further investigation (%)	38	(11)	41	(13)
Planned further investigation (%)	15	(4)	not asked	
Commenced medication (%)	120	(34)	106	(34)
bisphosphonate	23	(6)	21	(7)
alendronate	16	(4)	14	(5)
risedronate	7	(2)	7	(2)
calcium	103	(30)	93	(30)
vitamin D	22	(6)	21	(7)
Lifestyle changes (%)	232	(67)	218	(73)
increased dairy	197	(57)	169	(57)
increased exercise	85	(25)	95	(32)
reduced caffeine	8	(2)	17	(6)
reduced alcohol	8	(2)	13	(4)
reduced/stop smoking	11	(3)	13	(4)
other	19	(6)	15	(5)
Discussed with usual pharmacist about osteoporosis or osteoporosis medications (%)	not asked		63	(21)

Table 43 Knowledge score *before v after screening*

Knowledge score (/17)				Statistics
Before (n = 345)		After (n = 308)		
Median	Range	Median	Range	
10	(1-17)	14	(0-17)	Wilcoxon Rank: $z = -11.3$, $p < 0.0001$

Table 44 Knowledge questionnaire - Correct answers *before* vs *after screening*

	Before		After		Statistics
	n = 345 (%)		n = 308 (%)		
Q1*. One in two women and one in three men over 60 will develop an osteoporotic fracture	209	(61)	239	(78)	$\chi^2 = 11.8$ p = 0.0006
Q2. A family history of osteoporosis is not a risk factor for osteoporosis	126	(37)	206	(67)	$\chi^2 = 6.9$ p = 0.008
Q3. An early menopause, such as after a hysterectomy, is not a risk factor for osteoporosis.	104	(30)	192	(62)	$\chi^2 = 7.2$ p = 0.007
Q4*. A lifetime low intake of calcium will increase the risk of osteoporosis	227	(66)	248	(81)	$\chi^2 = 5.5$ p = 0.02
Q5. Smoking is not a risk factor for osteoporosis	174	(50)	217	(70)	$\chi^2 = 11.4$ p = 0.0007
Q6*. Thin women are more often affected by osteoporosis than heavy women	82	(24)	116	(38)	$\chi^2 = 22.2$ p < 0.0001
Q7* Weight bearing exercise such as walking can help prevent osteoporosis	265	(77)	266	(86)	$\chi^2 = 10.8$ p = 0.001
Q8. After age 40, it is too late for people to increase their calcium intake to prevent osteoporosis	217	(63)	243	(79)	$\chi^2 = 9.8$ p = 0.002
Q9*. After menopause, osteoporosis may be slowed down by taking oestrogen	164	(48)	204	(66)	$\chi^2 = 16.9$ p <0.0001
Q10*. All individuals lose bone mass after 40 years of age	223	(65)	226	(73)	$\chi^2 = 23.2$ p <0.001
Q11. Normally bone loss slows down after menopause	139	(40)	179	(58)	$\chi^2 = 19.7$ p <0.0001
Q12*. A diet high in calcium throughout life can help prevent osteoporosis	291	(84)	277	(90)	$\chi^2 = 14.0$ p = 0.0002
Q13*. Postmenopausal women need about 1000-1500mg of calcium each day	180	(52)	245	(80)	$\chi^2 = 14.7$ p =0.0001
Q14*. Dairy products are a major source of calcium	311	(90)	285	(93)	$\chi^2 = 0.1$ p = 0.7
Q15*. It is normal for bone loss to continue throughout life	203	(59)	194	(63)	$\chi^2 = 8.1$ p = 0.004
Q16. Active women are at higher risk for osteoporosis than inactive women	233	(68)	255	(83)	$\chi^2 = 0.7$ p = 0.4
Q17. Alcohol abuse is not linked to the incidence of osteoporosis	125	(36)	209	(68)	$\chi^2 = 5.5$ p = 0.02

n.b., answers were marked incorrect if not attempted, * statements that are 'true'

Characteristics of subjects referred to GP

In total, 191 subjects (55%) were referred to their GP for further assessment following the screening. Approximately 83% of subjects were referred because their QUS heel T-score was ≤ -1. Thirty-two subjects were referred to their GP for further evaluation despite having a T-score above –1. Fifteen subjects were referred because of previous low trauma fracture > 50 years, 8 subjects reported their parent breaking a hip and 9 subjects were currently receiving long-term (> 3 months) oral corticosteroids. Table 45 displays a comparison of the characteristics for subjects with T-scores above or below –1.

A comparison of the characteristics for subjects who had discussed their QUS result with their GP, compared to those who did not consult their GP, are shown in Table 46. In total, 68% of subjects consulted their GP and discussed their QUS results, with the majority (73%) having been referred by the pharmacist at the time of screening. Subjects were more likely to consult their GP if their QUS result was lower and there was a tendency for subjects with prior low trauma fractures to discuss their results further. Subjects consulting their GP were also more likely to commence medication than those who did not. Table 47 shows the characteristics of those commencing a medication following the screening, compared to those not commencing a medication following the screening.

Table 45 Characteristics of patients who were advised to consult their GP for consideration of further investigation* (T–score ≤ -1) compared to those not referred.

	Estimated BMD T-score				Statistics**
	Referred ≤-1.0 n = 159 (46%)		Not referred >-1 n =186 (54%)		
Age; years (median & range)	73	(65-91)	70	(65-88)	MW U = 11553, z = -3.5, p = 0.0005
Calcium intake; mg/day (median & range)	808	(69-3138)	821	(122-2258)	
Reports previous fracture (%)	40	(25)	28	(15)	χ^2= 5.3, p = 0.02
Reports loss of height – more than 2.5cm (%)	66	(52)	46	(38)	χ^2= 4.9, p = 0.03
Medication that increases risk of osteoporosis (%)	50	(31)	43	(23)	χ^2= 3.0, p = 0.08
BUA Z-score (median & range)	-0.2	(-2.1-2.7)	1.4	(-0.6-4.2)	MW U = 662.5, z = -15.0, p < 0.0001
5 year fracture risk (median & range, %)	10.7	(5.1-38.0)	4.8	(1.5-19.0)	MW U = 2574, z= -12.9, p <0.0001
Knowledge					
Before	9		10		MW U = 13455.5, z = -1.4, p = 0.15
After	13		14		MW U = 8696.5, z = -3.5, p = 0.0005
	Wilcoxon Rank: z = -6.2, p < 0.0001		Wilcoxon Rank: z=-9.5, p< 0.0001		
Sun score (median & range, /7)	4	(1-7)	5	(0-7)	MW U = 12772.5, z = -2.2, p = 0.03
Discussed results with GP (%)	121	(76)	112	(60)	χ^2 = 9.9, p < 0.002
Further investigation (%)	32	(20)	6	(3)	χ^2 = 25.0, p < 0.0001
Planned further investigation (%)	12	(9)	2	(1)	χ^2 = 11.9, p = 0.0006
Lifestyle changes (%)	71	(57)	74	(58)	p = not significant
increased dairy intake	90	(23)	107	(26)	
increased exercise	36	(4)	49	(2)	
reduced smoking	7	(3)	4	(2)	
reduced caffeine	4	(3)	4	(2)	
reduced alcohol	4	(4)	4	(2)	
other	7	(4)	12	(6)	
New medication commenced (%)	74	(47)	46	(25)	χ^2= 18, p < 0.0001
calcium	62	(39)	41	(22)	
vitamin D	12	(8)	10	(5)	
bisphosphonate	20	(13)	3	(2)	

*32 additional patients were referred to their GP with a T-score > -1 due to strong risk factors for osteoporosis: previous low trauma fracture > 50 years (n = 15), reports a parent breaking a hip (8), current corticosteroid use (9). **All χ^2 tests df = 1

Table 46 Comparison of characteristics of subjects who discussed QUS results with GP versus those who did not

	Discuss results with GP				Statistics*
	YES n = 233 (68%)		NO n =112 (32%)		
Age; years (median & range)	71	(65-90)	72	(65-91)	p = not significant
Calcium intake; mg/day (median & range)	862	(69-3138)	807	(123-1922)	MW U = 11807, z = -1.4, p = 0.15
Reports previous fracture (%)	51	(22)	17	(15)	χ^2= 2.2, p = 0.1
Referred by testing pharmacist (%)	140	(73)	51	(46)	χ^2= 6.5, p = 0.01
Number of regular medications (median & range)	4	(0-14)	3	(0-10)	MW U = 11410, z = -1.9, p = 0.06
Medication that increase risk of osteoporosis (%)	65	(28)	28	(25)	χ^2= 0.3, p = 0.6
corticosteroids	17	(7)	3	(3)	χ^2 = 3, df = 1, p = 0.09
Estimated BMD T-score (median & range)	-1.1	(-3.0-1.9)	-0.6	(-2.5-1.5)	MW U = 10035, z = -3.5, p = 0.0005
<-1.8 (%)	59	(25)	10	(9)	
<-1 (%)	121	(52)	38	(34)	
5 year fracture risk (median & range, %)	7.3	(1.5-35.9)	5.8	(1.7-38.9)	MW U = 10166.5, z = -2.5, p = 0.01
Knowledge					
Before	10	(1-17)	9	(1-16)	MW U = 11645, z = -1.6, p = 0.2
After	14	(0-17)	13	(0-17)	MW U = 8819, z = -1.6, p = 0.1
Sun score (median & range, /7)	5	(0-7)	5	(1-7)	p = not significant
Lifestyle changes (%)	168	(72)	64	(57)	χ^2= 7.7, p < 0.006
increased dairy intake	144	(62)	53	(47)	
increased exercise	61	(26)	24	(21)	
reduced smoking	9	(4)	2	(2)	
reduced caffeine	3	(1)	5	(4)	
reduced alcohol	4	(2)	4	(4)	
other	15	(6)	4	(4)	
New medication (%)	109	(47)	11	(10)	χ^2= 45.6, p < 0.0001
calcium	93	(40)	10	(9)	
vitamin D	18	(8)	4	(4)	
bisphosphonate	23	(10)	0	(0)	

*all χ^2 tests df = 1

Table 47 Characteristics of patients commencing a medication to treat or prevent osteoporosis following screening

	Patients commencing anti-osteoporotic medication n = 120 (%)		Patients not commencing anti-osteoporotic medication n = 225 (%)		Statistics
Age; years (median & range)	71	(65-90)	71	(65-91)	
Education (%)					$\chi^2 = 8.0$, df = 4, p = 0.09
no formal schooling	1	(1)	3	(1)	
primary school	71	(59)	119	(53)	
high school	40	(33)	67	(30)	
technical qualification	5	(4)	31	(14)	
university	3	(3)	5	(2)	
Body mass index; kg/m^2 (median & range)	27	(18-43)	27	(16-47)	
Number of chronic medications (median & range)	3	(0-10)	4	(0-12)	MW U = 12745.5, z = -0.9, p = 0.4
Medications that increase risk of osteoporosis (%)	40	(33)	53	(24)	$\chi^2 = 3.8$, df = 1, p = 0.05
Medications that increase risk of falls (%)	88	(73)	177	(79)	$\chi^2 = 1.25$, df = 1, p = 0.3
Self-reported risk factors for osteoporosis (%)	74	(70)	139	(71)	p = not significant
Previous fracture (%)	21	(19)	39	(20)	
Calcium intake; mg/day (median, range)	709	(242-2032)	901	(69-2392)	MW U = 10149.5, z = -3.8, p = 0.0001
0-499 mg (%)	23	(19)	35	(15)	
500-999 mg (%)	70	(58)	96	(43)	
1000-1499 mg (%)	20	(17)	61	(27)	
≥1500 mg (%)	7	(6)	33	(15)	
T-score (median & range)	-1.3	(-2.9-1.5)	-0.6	(-3.0-1.9)	MW U = 9257.5, z = -4.8, p <0.0001
T ≤-1.8	36	(30)	33	(15)	
T >-1.8<-0.5	62	(52)	97	(43)	
T ≥-0.5	22	(18)	95	(42)	
BUA Z score (median)	0.1	(-2.1-3.8)	1	(-2.1-4.2)	MW U = 8627, z = -4.9, p < 0.0001
Z-score < 0 (%)	47	(40)	45	(21)	
Z-score < 1 (%)	16	(14)	9	(4)	
5 year fracture risk (median & range, %)	8.2	(1.5-32.5)	6.0	(1.6-38.9)	MW U = 9173.5, z = -4.3, p = 0.0001
Knowledge score; /17 (median & range)	10	(1-17)	9	(1-17)	MW U = 12682, z = -0.9, p = 0.4
Discussed results with GP (%)	109	(90)	124	(55)	$\chi^2 = 45.0$, df = 1, p < 0.0001
Further investigation (%)	26	(22)	12	(5)	$\chi^2 = 21.3$, df = 1, p<0.0001
Lifestyle changes (%)	91	(76)	141	(63)	$\chi^2 = 6.2$, df = 1, p =0.01

Commencement of anti-osteoporotic medications

A total of 120 subjects (34%) from the phone survey indicated that they had commenced a medication following the screening. Of these, 6% indicated that they had commenced a bisphosphonate (alendronate 4%, risedronate 2%). Approximately 30% of all subjects indicated they had commenced a calcium supplement and 6% indicated they had commenced a vitamin D supplement. No subject commenced raloxifene, hormone replacement therapy or calcitriol. There was no difference between subjects commencing a new anti-osteoporotic medication if they reported a previous fracture or not, 19% vs 20% respectively (p = not significant). However bisphosphonates were more likely to be prescribed if subjects had reported a previous fracture, 18% v 4% (χ^2= 16.4, df = 1, P < 0.0001). There was no difference in use of calcium (28% v 30%, χ^2= 0.1, df = 1, p = 0.7) and vitamin D (3% v 7%, χ^2= 1.7, df =1, p = 0.2) if the subject reported a previous fracture or not.

Calcium supplements

Approximately 30% of subjects who had screening performed commenced a calcium supplement. The overwhelming majority of these had a low calcium intake when questioned at the screening. In fact, 21% (n = 22) and 60% (n = 62) of subjects starting calcium supplements had a calcium intake less than 500 mg/day or between 500 mg and 1000 mg/day respectively. Only 6 subjects (6%) who started a calcium supplement had a calcium intake above 1500 mg/day.

Subjects commencing calcium supplements had a lower median estimated BMD T-score compared to those not commencing calcium supplements (-1.3, range: -2.9-1.5 v -0.7, range: -3.0-1.9; MW U = 9186.0, z = -3.9, p = 0.0001). The 5-year fracture risk in

subjects commencing calcium was significantly higher (8.2%, range: 1.5-32.5) than rs after an osteoporotic fracture</TITLE><SECONDARY_TITLE>Ann Rheum Dis</SECON= 8910, z = -3.6, p = 0.0004). The majority (90%) of subjects commencing calcium supplcmcnts had discussed their osteoporosis screening result with their usual doctor. Three-quarters (78%) of subjects commencing calcium supplements had also made lifestyle changes following the screening. This was significantly more than those who did not commence calcium supplements (62%) ($\chi^2 = 7.2$, df = 1, p = 0.007).

Vitamin D supplements

Approximately 6% (22 patients) commenced a vitamin D supplement following the screening. There was no difference in the sun score between subjects who commenced vitamin D (median sun score = 5) or those who did not (median sun score = 5). Fifteen subjects (68%) who commenced a vitamin D supplement also commenced a calcium supplement. The median T-score in those patients commencing a vitamin D supplement was –1.3 (-2.9-0.4), compared to –0.8 (-3.0- 1.9) in those subjects not commencing a vitamin D supplement (MW U = 3018, z = -1.1, p = 0.24). The 5-year fracture risk in those subjects commencing vitamin D was 6.9% (3.2-32.5), which was identical to subjects not commencing vitamin D who also had a 5-year fracture risk of 6.9% (1.5-38.9).

Eighteen subjects (82%) had discussed their screening results with their doctor prior to commencing vitamin D supplements. Subjects commencing vitamin D supplements were *more* likely to make lifestyle changes than those not commencing vitamin D, 68% v 32%, although due to small numbers commencing vitamin D this was statistically insignificant ($\chi^2 = 0.009$, df = 1, p = 0.9).

Bisphosphonates

The median heel estimated BMD T-score for those subjects commencing a bisphosphonate was significantly lower than those not started on a bisphosphonate (median T-score = –1.9 [-2.9-0] vs -0.7 [-3.0-1.9]; MW U = 1558.5, z = -4.6, p < 0.0001). Subjects commencing a bisphosphonate were at 2-fold increased risk for fracture in the next five years compared to subjects not commencing bisphosphonates. The 5-year fracture risk in subjects commencing a bisphosphonate was 12.4% (range: 2.9-32.2) compared to 6.5% (range: 1.5-38.9) in those not commencing a bisphosphonate (MW U = 1882.5, z = -3.3, p = 0.0009). The median daily calcium intake of subjects commencing a bisphosphonate was 974 mg (420-1948 mg).

Lifestyle changes

The majority (67%) of subjects stated in the phone survey (73% postal survey) that since the screening, they had made lifestyle changes. This included mostly increasing their dairy intake. In fact, 57% and 25% phone survey of subjects stated they had increased their calcium intake and exercise, respectively. Other lifestyle changes (6%) included: increasing fruit and vegetable intake, increasing fish intake, or changing from full cream milk to low fat milk. Table 42 shows the breakdown of lifestyle changes made by subjects.

Subjects were significantly more likely to report an increase in dairy intake if they had a lower calcium intake at the screening. The median calcium intake in those people stating they increased their dairy intake was 771 mg (128-2032 mg) compared to those who had not increased their dairy intake which was 1023 mg (69-2392 mg), {MW U = 7889, z = -4.2, p< 0.0001}. There was no difference in baseline knowledge score in

those subjects reporting lifestyle changes versus those who did not report altering their lifestyle (MW U = 13097, z = -0.013, p > 0.9).

Characteristics of subjects by age

There were differences between older and younger women's characteristics and these are shown in Table 48. Women aged over 75 years were more likely to have a lower calcium intake (722 mg v 897 mg daily) although they were no more likely to commence calcium supplements (χ^2 = 1.3, p = 0.3). Older subjects had a significantly lower median estimated BMD T-score compared to their younger counterparts (-1.2 v – 0.6; MW U = 8480, p <0.0001). Older subjects were more likely to report a previous fracture than younger subjects (27% v 17%; χ^2 = 4.6, p = 0.03).

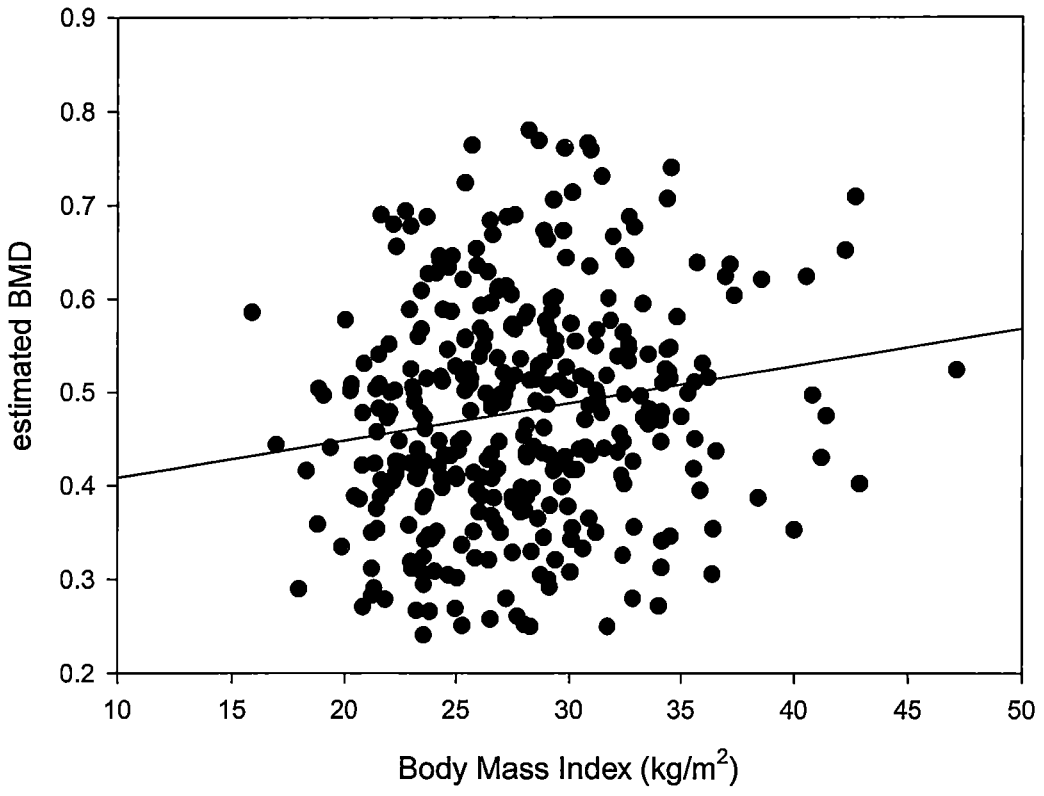
Table 48 Comparison of the characteristics of subjects aged 65-74 years and 75 years or above

	Age (years)				Statistics
	65-74 (n=249)		75+ (n = 96)		
Calcium intake; mg/day (median & range)	897	(69 - 3138)	722	(128 - 1767)	MW U = 9527, z = -2.9, p = 0.004
Estimated BMD T-score (median & range)	-0.6	(-2.9 - 1.9)	-1.2	(-3.0 - 1.8)	MW U = 8480, z = -4.2, p < 0.0001
< -1.8	38	(15)	31	(32)	
< -1	98	(39)	61	(64)	
Previous fracture (%)	42	(17)	26	(27)	χ^2 = = 4.6, df = 1, p = 0.03
BUA Z-score (median and range)	0.9	(-2.1 - 4.2)	0.2	(-2.1-3.6)	χ^2 = 11.3, df =1, p = 0.0008
<0 (%)	60	(24)	32	(37)	
<-1 (%)	15	(6)	10	(11)	
Five year fracture risk (median & range, %)	5.6	(1.5-20.5)	14.9	(3.5-38.9)	MW U = 2110, z = -11.2, p <0.0001
Knowledge					
Before	10	(1-17)	8	(2-15)	MW U = 8774, z = -3.8, p .0001
After	14	(0-17)	12	(0-17)	MW U = 5642.5, -4.8, p < 0.0001
	Wilcoxon signed rank: z = -10.2, p < 0.0001		Wilcoxon signed rank: z = -5.0, p < 0.0001		
Sun score; /7 (median & range)	5	(1-7)	4.5	(0-7)	MW U = 11063, z = -1.1, p = 0.3
Lifestyle changes (%)	171	(69)	61	(64)	χ^2 = = 0.8, df = 1, p = 0.4
increased dairy intake	139	(56)	58	(50)	
increased exercise	63	(25)	22	(23)	*Note:* some subjects made more than one lifestyle change.
reduced smoking	7	(3)	4	(4)	
reduced caffeine	6	(2)	2	(2)	
reduced alcohol	6	(3)	2	(2)	
other	14	(6)	5	(5)	
Commenced medication (%)	84	(34)	36	(37.5)	χ^2 = = 0.4, df = 1, p = 0.5
calcium	70	(28)	33	(34)	
vitamin D	20	(8)	2	(2)	
bisphosphonate	15	(6)	8	(8)	

Figure 36 shows a weak, but statistically significant correlation between body mass index and estimated heel BMD.

Figure 36 Correlation between estimated heel BMD and body mass index

Rho = 0.181, z = 3.35, p = 0.0008, Y= -1.821 + 0.036x, r2 = 0.028



Subject satisfaction

Almost 90% of subjects (n = 308) completed and returned a follow-up survey (Table 49). Subject comments are shown in Appendix 15.

Table 49 Subject satisfaction with the screening programme

	Number of Responses	(%)
Did you find the osteoporosis screening useful?		
Yes – helped a great deal	*167*	*56*
Yes – helped somewhat	*97*	*32*
No – not really	*20*	*7*
No – not at all	*2*	*1*
Unsure	*14*	*4*
Has the information and other services you received from the pharmacist (Mark Naunton) helped?		
Yes – helped a great deal	*140*	*48*
Yes – helped somewhat	*101*	*35*
No – not really	*30*	*11*
No – not at all	*7*	*2*
Unsure	*11*	*4*
Should this service be available to all women over 65 years of age?		
Yes	*279*	*93*
No	*3*	*1*
Unsure	*18*	*6*
Would you be willing to pay for this service?		
Yes	*133*	*46*
No	*79*	*27*
Unsure	*76*	*27*
How many dollars would you be willing to spend? (median and range from 84 responses)	*20 (5-100)*	
How would you rate the quality of service you received from the pharmacist (Mark Naunton)?		
I can't remember	*3*	*1*
Poor	*1*	*0*
Good	*45*	*15*
Very good	*87*	*29*
Excellent	*164*	*55*
Do you feel your doctor was happy with the screening?		
Yes – definitely	*105*	*41*
Yes – I think so	*82*	*32*
No – I don't think so	*5*	*2*
No – definitely not	*1*	*1*
Unsure	*61*	*24*

Note: not all subjects responded to each question

GP satisfaction

There was a total of 47 GPs who had subjects present to the pharmacies for screening. The GP satisfaction survey (response rate 60%) results are shown in Table 50. The doctors displayed varied opinions on the screening project. Appendix 16 displays comments from GPs. Three GPs who responded to the survey (11%) indicated that they had encountered problems/difficulties with patients following the screening; their comments are highlighted in Appendix 16.

Table 50 GP satisfaction survey

	Visual analogue scale (0-10)	
	Median score	**Range**
Were you fully informed of the project prior to its commencement? (0 = no not at all, 10 = yes completely)	9	0-10
Did you receive adequate feedback (by letter or phone) from the pharmacist performing the screening? (0 = not adequate, 10 = more than adequate)	9	0-10
Do you believe that your patients found the osteoporosis screening useful?(0 = not useful, 10 = very useful)	7.25	2-10
Did you find the osteoporosis screening useful? (0 = not useful, 10 = very useful)	5	1-9.5
Would you support more widespread use of osteoporosis screening in pharmacies if the pharmacist is adequately trained and there are specific guidelines to follow? (0 = not support at all, 10 = strongly support)	5	0-10
Do you believe pharmacists can assist doctors identify patients at risk of osteoporosis? (0 = not at all, 10 = most definitely)	6.75	1.5-10

Pharmacist satisfaction

Eight of the 12 pharmacists returned satisfaction surveys (response rate 75%) and the results are shown in Table 51. Pharmacists' comments are shown in 17. There were no comments from pharmacists indicating problems or difficulties following the screening.

Table 51 Pharmacist satisfaction survey

	Visual analogue scale (0-10)	
	Median score	**Range**
Were you satisfied with the pharmacist (Mark Naunton) conducting the osteoporosis screening in your pharmacy? (0 = not at all, 10 = yes completely)	9.5	9.5-10
Did you find the osteoporosis screening useful? (0 = not useful at all, 10 = very useful)	9.5	7-10
Do you believe that your patients found the osteoporosis screening useful? (0 = not useful at all, 10 = very useful)	9	7-10
Do you believe that your local doctors found the osteoporosis screening useful? (0 = not useful at all, 10 = very useful)	7.8	5-10
Do you believe pharmacists can assist doctors identify patients at risk of osteoporosis? (0 = not at all, 10 = most definitely)	9.5	7-10

Cost benefit analysis

The costs and savings from conducting a widespread screening programme are shown in Table 52. In summary, if a widespread programme, as used in this study was rolled out nationwide, it is not likely to show a cost-benefit. In fact, each year it could be expected to cost an additional $9 million even if the subject pays $40 to have the screening performed. The cost of screening and treatment as they currently stand, exceeds any potential savings, based on reduced fractures alone.

Table 52 Cost-benefit of screening for osteoporosis in Australian women > 65 years in community pharmacies

	5-yearly $Aust (million)	
	Cost	Savings
Cost of screening[a]		
Cost of machine and expendables	0.5	
Cost of screening without patient contribution (@ $40 each)	52.0	
Cost of screening with patient contribution ($20 each)	26.0	
Cost of treatment[b]		
Cost of treating women commencing bisphosphonate (@$60 per month)	224.6	
Cost of treating women with calcium (@$6.30 per month)	147.4	
Total treatment costs	372.1	
Total costs (cost of screening and treatment)		
Total costs if no patient contribution	424.6[j]	
Total costs if patient contribution of $20	398.6[k]	
Total costs if patient pays $40	372.6[m]	
Costs associated with osteoporotic fractures[c]		
Cost of fractures	2107.5	
Cost of fractures in women > 65 years[d]	1686.0[x]	
Cost if 6% on bisphosphonates and achieve 50% reduction in risk[332]	1635.4	
Savings related to reduced cost of osteoporotic fractures with bisphosphonates		50.6
Cost if 30% on calcium and achieve 25% reduction in risk[332]	1559.5	
Savings related to reduced cost of osteoporotic fractures with calcium		126.4
Savings related to calcium and bisphosphonates		**177.0**
New cost (after adjustment for savings) in women > 65years	1508.9	
But if calcium and bisphosphonate treated patients are those at highest risk and account for 66% of the cost of fractures in these women[e]		
New cost in these women > 65years	1358.2[y]	
Savings (x-y)		327.8[z]
Total savings if no patient contribution (5 years)		**-96.8[z-j]**
Total savings if patient pays $20 (5 years)		**-70.8[z-k]**
Total savings if patient pays $40 (5 years)		**-44.8[z-m]**

a. Assume screening 1.3 million Australian women >65 years (2001 data from Australian Bureau of Statistics).

b Assume 6% of women screened commence a bisphosphonate and of these, 20% discontinue, also assume 30% of women screened commence calcium supplement. Costs based on PBS rebate as at February 2004 for alendronate 70 mg once a week and calcium carbonate 600 mg twice daily.

c Cost attained from Access Economics ($421.5 million per annum) and only include costs directly attributable to osteoporotic fractures and exclude other costs such as kyphosis, back problems and all osteoporosis from secondary sources[183].

d Women over 60 years account for 80% of costs associated with osteoporotic fractures (Kerrie Saunders, personal communication).

e Assume 66% of women treated with calcium or bisphosphonates are those at highest risk and therefore account for the majority of the costs associated with osteoporosis.

Chapter 4: Discussion

Screening for any disease will only be of value if actions are undertaken either by the individual or by their treating doctor. One hundred and ninety one (55%) women were referred to their doctor, and 140 of these actually visited and discussed their results with their doctor. Of these 34 (24%) were further investigated by central DEXA. The majority (70%) of subjects who underwent further testing were then prescribed a medication, strongly indicating that they were correctly identified at high risk. Elliot *et al*[426] had similar findings, with 27% of subjects discussing their results with their GP and having a further central DEXA assessment. Of the subjects who had further testing, 67% received prescription treatment and 16% was treated with "over the counter" medication. Overall, one-third (34%) of patients screened commenced a medication to treat or prevent osteoporosis.

Calcium supplements were the most common medication commenced (and increasing dairy intake was the most common lifestyle change) in patients following the screening. Bisphosphonates were commenced in 6% of subjects and vitamin D was commenced in 6% of subjects as well. Subjects commencing calcium supplements or bisphosphonates had a significantly higher 5-year fracture risk.

An interesting finding was that 60% of subjects who were not referred to their GP in fact did discuss their screening results. It was pleasing though, that only 4 subjects were further investigated and two subjects subsequently treated. The most likely explanation for the high number of women consulting their doctor and discussing their results further (based on anecdotal reports from subjects at follow-up) is that they had an appointment to see their doctor for other reasons (e.g., prescription renewal was often cited), although this cannot be formally substantiated.

In studies where women received hip and spine DEXA measurements, BMD testing led to changes in therapy and lifestyle[495-498]. Elliott *et al*[426] found in their educational intervention with peripheral DEXA testing, that approximately 20% of subjects commenced a therapy for the treatment or prevention of osteoporosis. Recent, but unpublished research, demonstrated that individualised BMD feedback combined with a minimal educational intervention was effective at increasing hip bone density in premenopausal women[499]. Our study showed that QUS measurements also led to intervention, particularly in those found to be at risk. Subjects who commenced treatment or prevention generally had a significantly higher 5-year fracture risk (8.2%) than those who did not commence a medication (6.0%).

The majority of subjects in this study were not receiving the recommended calcium intake, with approximately 15-20% ingesting less than 500 mg of calcium a day. In fact, only 10-15% of subjects were receiving 1500 mg or more of calcium/day. The median intake of calcium in those women taking calcium supplements was 1336 mg/day which was identical to the study conducted by Elliot *et al*[481] who found the mean calcium intake in patients undergoing osteoporosis screening in a community pharmacy was 1333 mg/day. The median oral intake of older women (75+ years) was significantly less than women aged 65-74 years (722 mg v 897 mg; $p = 0.004$). It has been previously shown that the elderly often have poor nutrition[500]. Despite having a lower calcium intake and lower T-score, women over 75 years were no more likely to commence any new medications or make lifestyle alterations than those aged 65-74 years. This is somewhat disappointing given that this age group is at higher risk for fracture[182].

The cohort of subjects had a higher calcium intake than was found in the Australian Nutrition Survey in 1995[501]. In that study, women over 65 years of age had an average daily calcium intake of 685 mg. Subjects in this study had a median intake of

812 mg/day which is consistent with other studies conducted in Australia and North America demonstrating calcium intakes are often below the recommended intake[502]. In a similar screening intervention in Wisconsin (United States), Elliot *et al*[481] found elderly subjects had a mean daily intake of 862 mg/day. This is despite the fact that 56% of the participants took calcium supplements, compared to 16% in this study. The overwhelming majority of subjects commencing calcium supplements in this study had a low calcium intake, suggesting that the majority of women were not unnecessarily commencing them. In fact, only 6% of patients who initiated calcium supplements had a calcium intake of over 1500 mg.

Vitamin D supplements were also commenced in 6% of subjects undergoing screening. It is not surprising that so few subjects commenced vitamin D supplements considering the median sun score was 5, which suggests subjects involved in the screening programme were not at high risk for vitamin D deficiency. The subjects commencing vitamin D tended to have a higher risk for osteoporosis (T = -1.3) than the general study population (T=-0.8). The vast majority of subjects (82%) commencing vitamin D had discussed the screening with their GP.

Inderjeeth *et al*[490] found that the average sunscore in women with vitamin D deficiency (defined in their study as plasma level <28 nmol/L) was 3.7 and the median age of these patients was 80 years. In contrast, subjects without vitamin D deficiency (>28 nmol/L) had a mean sunscore of 4.7 (and the median age was 76 years). Further analysis of our data (data not shown) showed that women aged over 80 years had the same sun score (median = 5) as those aged from 65-79 years. It can therefore be concluded that women in our study were likely to be at low risk of vitamin D deficiency. Inderjeeth *et al*[490] found a low incidence of vitamin D deficiency in active elderly

subjects, which best describes our study population, although we did not formally assess level of exercise.

There was no difference in sun score between subjects aged 65-74 and aged 75 years and over. Studies locally[490, 503], nationally[504] and internationally[505, 506] have shown that vitamin D deficiency is common in the frail and institutionalised elderly. Younger groups[507] and active older groups[490] have not been found to be vitamin D deficient.

Health fairs have been shown to be an effective setting for identifying patients with osteoporosis by heel ultrasound[492]. There is some evidence that osteoporosis screening using QUS at shopping centres can promote lifestyle change (increased calcium intake) in subjects undergoing the screening[508].

This screening intervention also appeared to promote lifestyle changes, with approximately two-thirds stating they had modified their lifestyle to reduce their risk of osteoporosis. Approximately half of patients (57%) stated they had increased their calcium intake with those reporting increasing their dairy intake having a statistically lower median calcium intake (771 mg v 1023 mg; $p < 0.0001$). It was especially pertinent that one-quarter (25%) of patients declared that they had increased their level of exercise, given that 66% of subjects were over-weight (36%) or obese (30%). Some patients made lifestyle changes, independent of their screening results.

Anecdotally, one subject sold her ride-on lawnmower for a push lawnmower. Another subject found to be at low risk, had a body mass index of 34 kg/m^2 and did not realize that she was in the obese category. This prompted her to embark on a fitness programme that reportedly yielded a 10 kg loss in mass three months later. Although this was encouraging, overweight or obese subjects were no more likely to report an increase in exercise than subjects with a "normal" body mass index or low estimated heel T-score. Even so, this study highlights that pharmacists may be ideally placed to counsel

and advise patients on weight loss. A successful weight loss management programme that was conducted in a community pharmacy in the United States has recently been published[79].

Pazirandeh *et al*[509] found that educating patients and doctors about osteoporosis resulted in more BMD tests being ordered, although the patients initiated discussion more than their doctors (60% v 18%). However, this may not be able to be generalised as the subjects were schoolteachers and perhaps more motivated than the general population. A recently completed (submitted for publication) study by Winzenberg[499] conducted in Tasmania, also showed an increase in subjects' lifestyle behaviour following a BMD feedback and educational intervention. The investigators demonstrated an increase in BMD, mediated through changes in physical activity and calcium supplement usage alone.

Rolnick *et al*[510] found that education regarding osteoporosis prevention seems to encourage women to make lifestyle changes and the inclusion of BMD testing enhanced the likelihood that women will consider pharmaceutical therapy. This study has also have found that education and screening for osteoporosis appears to increase self-reported lifestyle changes, although caution is required when interpreting these findings due to a non-validated method for reporting changes and relying on simple self-report. Other uncontrolled studies have suggested that BMD screening increases self-reported osteoporosis preventive behaviour at 12 months; in women aged 30-80 years[511] and in premenopausal women[498, 512] in particular, greater changes were reported in women with low BMD. However, not all studies[513-515] have reported subjects make lifestyle modifications following educational interventions, although Brecher *et al*[516] reported their participants were more likely to consider making behavioural changes.

Although our study was not designed to study bone changes, it is encouraging that simple educational interventions can positively influence subjects' self-reported behaviour. Winzenberg and colleagues[499] found that women receiving feedback of a low T-score result were more likely to commence calcium supplements and to report changes in physical activity, as well as have greater increases in BMD, compared to women with a high T-score. In contrast, our subjects who had a low T-score (<-1) were no more likely to make lifestyle changes than those with a T-score >-1 ($p > 0.05$). The reasons for this are unclear, but may be related to the comprehensive counselling of all subjects on the importance of physical activity and a diet high in calcium for their bone health.

Patients also reported that they had reduced or ceased smoking, and other changes such as swapping to low fat (high calcium milk) and increasing their consumption of vegetables. Winzenberg *et al*[499] also reported changes in premenopausal women's' smoking habits. The behavioural changes achieved in this study could also be potentially beneficial for prevention of other chronic diseases that could be reduced by increased calcium intake and/or increased physical activity, such as cardiovascular disease, obesity and diabetes.

It was pleasing that three months post-screening, the womens' knowledge overall was significantly increased (from a median 10/17 to 14/17). Knowledge increased across all aspects of the questionnaire. Women aged over 75 years had a significantly lower osteoporosis knowledge than their younger counterparts at baseline, but increased significantly (as did the younger women) at follow-up. A previous study demonstrated womens' knowledge was limited and was not associated with age[517]. Perhaps of concern was that only a third of women following the intervention agreed with the statement "Thin women are more often affected by osteoporosis than heavy women". This may be

due to the fact that many women found to be at potential risk were overweight in our study. However, there appeared to be a view from the subjects that heavy women were at higher risk because there was "more weight on the bones" and thus may weaken the bones. Many women were also confused with the role of HRT and its effect on bone. Due to the release of the Women's Health Initiative in 2002[290] and the Million Women Study in 2003[518] many women thought HRT was not of benefit at all (including preventing bone loss) with one women stating that "hormones are not good for anything anymore so they tell us".

Despite having low calcium intake, the subjects in the study had a high level of understanding on the importance of calcium to bone health. Approximately 66% of women correctly answered the statement "A lifetime low intake of calcium will increase the risk of osteoporosis" and 63% correctly answered "After age 40, it is too late for people to increase their calcium intake to prevent osteoporosis". Furthermore, 84% of women correctly answered, "A diet high in calcium throughout life can help prevent osteoporosis".

In spite of having an adequate knowledge on the importance of calcium to bone health, it appears many women do not know how much calcium they require. Only 52% of women correctly answered the statement "Postmenopausal women need about 1000-1500 mg of calcium each day". However, more importantly 83% (from the 308 returned surveys) of the women could answer the same statement correctly following the screening. Hence, the screening programme had a significant impact on women's knowledge of daily calcium requirements. Inadequate calcium intake by the vast majority of women in this research suggests that further efforts are required to improve the calcium status in elderly rural women.

A somewhat disappointing outcome from this intervention was that subjects reporting a previous low-trauma fracture were overall no more likely to receive therapy than those without prior fractures. It has been well established that a previous fragility fracture is a high predictor for any future fractures[182, 519]. In fact, our subjects with a previous fragility fracture were shown to have a significantly higher predicted 5-year fracture risk than those without a previous fracture, 9% v 6.3% ($p = 0.004$). It was encouraging that patients were more likely to receive a bisphosphonate if they had reported a prior low trauma fracture. However, this is not surprising given that the PBS allows GPs to prescribe bisphosphonates (and raloxifene) at subsidised rates if the patient has sustained a low trauma fracture or suffered a 20% reduction in vertebral height which has been demonstrated radiologically[520]. Even so, it was still a reasonably low proportion of women (18%) who reported a previous fracture and received a bisphosphonate. It must be borne in mind that women were more likely to discuss their results with their doctor if they reported a previous fracture (75% v 66%, $p = 0.14$) and were twice as likely to have further investigations performed (18% v 9%, $p = 0.05$) than those who did not report a previous fracture. Nonetheless, there were a large number of women screened who would have qualified under the PBS scheme for a bisphosphonate (or raloxifene) and were not treated.

It is well documented that osteoporosis is a major societal health issue that even when recognised is not acted upon[521]. Family physicians in a recent Canadian study[522] reported that one of the most influential factors affecting the decision to order a BMD test was "risk factors for osteoporosis". Recent fracture, one of the most important predictors of osteoporosis, was less influential than other risk factors in influencing the ordering of a BMD test. The authors discussed that the importance of prior fracture for future fracture is not well known by most family physicians. It has also been shown in

other studies in Canada that most patients who suffer a fragility fracture do not receive a subsequent diagnosis of osteoporosis or any treatment[45, 523, 524].

The reasons for this apparent undertreatment are probably multifactorial and include patient, doctor and health-care system. For example, the GP is required to provide the date of fracture when prescribing a bisphosphonate and this may have not been readily available at the time of consultation. An Australian study has also recently shown that few patients receive treatment following a low trauma fracture[525]. The authors concluded that the implementation of a clinical pathway for osteoporosis management in these patients might be useful. Hawker *et al*[324] demonstrated that following the implementation of a fracture clinic, individuals (with a fragility fracture) were more likely to be followed up by their doctor and be offered a BMD but were no more likely to receive osteoporosis treatment. This suggests more education of doctors is required on the benefits of treating osteoporosis.

Some GPs perhaps missed the point or showed a lack of understanding of the screening programme with one GP stating, "trouble is – all patients identified at risk tend to need formal DEXA testing anyway". This is exactly the argument *for* pre-screening with QUS; that those at *highest risk* go on to formal DEXA testing. Another stated "people pay money for one heel screening. It provides a guide only. They then need to pay again to have a diagnostic BMD done and maybe an x-ray to look for a fracture. It adds to the cost for little benefit." The GP in this case also shows a lack of thought to the purpose of screening. Subjects shown to be at low risk do not necessarily need to be further investigated, as the GP appears to infer. Other GPs suggested that the reason they did not investigate further was because that some patients would not qualify for subsidised treatment under the PBS, for example, bisphosphonates. However, it

should be mentioned that some women are prepared to pay fully for osteoporosis treatment themselves.

During discussions with the subjects undergoing screening, there were women in the study who were prepared to pay privately for expensive medications if they did not qualify for a government subsidy. Women's willingness to pay for "out of pocket" for drug treatment has previously been considered[526]. In a study by Werner *et al*[526], women were prepared to pay from 54-100% of the price of the drugs (depending on the level of risk). It is also worth considering that women will make lifestyle changes following BMD measurements, and this has been reported (unpublished) to increase BMD[499].

One GP in the study also felt that if some women did not qualify for subsidised treatment, it created "anxiety and illness behaviour". However, this GP also criticised the project and stated "don't do it unless you supply prospective studies and treatment options that are affordable" - clearly disregarding the fact that calcium and vitamin D are inexpensive options in the prevention of fractures in elderly women and furthermore disregarding the usefulness of QUS at predicting fracture as shown in prospective studies[425, 444, 452, 456, 465, 527, 528]. A GP also stated that subjects "would be better to be advised to talk to their doctor about diagnosis for fractures and appropriate prevention". Again, the GP is perhaps ignorant of the usefulness that QUS has and the role it can potentially fulfil in detection of patients at risk of osteoporosis. On the other hand, the GP may believe pharmacies are not an ideal place to conduct screening. Our results suggest this is not the case and that with correct training and education, a community pharmacy is an ideal place to conduct osteoporosis screening. More research is required on GPs' views and knowledge on QUS and its role in the management of osteoporosis.

A recent study in the United Kingdom reported that most GPs receive an inadequate exposure to teaching on osteoporosis at medical school[529]. A recently

published study found that GPs find it difficult to decide who and when to refer for DEXA scans despite guidelines for primary care[530]. Given that GPs have difficulty screening with the "gold standard" it cannot be expected that they will necessarily know the position QUS has in primary care and this will require widespread dissemination once firmly established as a useful method to assess women risk for osteoporosis.

It is possible that some subjects given information at the screening consulted their GP with an anticipation of prescription medication when it was not indicated. One GP commented in their returned survey that there was "unrealistic expectation with regard to possible treatments". Every effort was made by the pharmacist to inform subjects of their eligibility for medications and possible costs involved, however it was accepted as a possible barrier that GPs would face in dealing with some patients anticipating prescription medication. On the other hand there were reports from subjects who refused any treatment offered by their GP. General practitioners appear positive towards pharmacists educating patients about osteoporosis and referring them to GPs for further discussion and/or investigation, even if they appeared uncommitted with more widespread screening by pharmacists for osteoporosis. Despite this, there were GPs who were very supportive of the screening and some GPs showing thoughtful comments such as "although there are some limitations with heel ultrasound and screening in general, I found this service beneficial to me and my patients".

There were cases where there appeared to be "negligence" towards women who had undergone screening as shown in the example below (Box 5). Another woman (T-score –1.5) stated at follow-up that she "asked for a bone scan but was refused" a referral for further investigation.

Box 5 An example of possible GP "negligence"

A 73 year old woman (BMI = 24.7 kg/m^2) who was currently being treated with 11 medications (6 regular medications) including paracetamol/codeine combination and diclofenac for back pain stated at follow-up her GP "didn't seem interested" in her results. The woman had a strong family history of osteoporosis, including her sister and son, reportedly had a 7cm loss in height, and had multiple low-trauma fractures (including a recent rib fracture from coughing). Her estimated BMD T-score was –2.3 and she had a 5-year fracture risk of 13.7% (usual risk = 9.1% for her age).

There were no known contraindications for this woman to receive a bisphoshonate (although she was treated with omeprazole for "indigestion"), raloxifene, calcium or vitamin D, yet she received no treatment from her doctor even when directly asking for it and was told she would not qualify for treatment.

In another study conducted in Canada, Jaglal *et al*[531] found that physicians did not know enough about pharmacologic treatment of osteoporosis. Family physicians in England had similar gaps in knowledge as exposed by Taylor *et al*[529] who reported that education on osteoporosis for GPs is considered inadequate. When asked what kind of information they would like, almost 90% of GPs wanted information on prevention and treatment. It is possible that the low rate of prescribing of bisphosphonates and treatments in general in our study may be due to a lack of clinical knowledge and management of osteoporosis.

A study conducted in Israel showed that physicians had relatively little knowledge about adequate dosages of drugs other than oestrogen. These findings highlight that doctors' knowledge of appropriate treatments need to be increased. It is also interesting that some GPs remain unconvinced about the benefit of osteoporosis drug therapy[529], despite effective drug therapy offering a 50% reduction in fracture

risk[274, 377, 387]. It is reasonable to assume that some GPs in this study were unconvinced of treatment, particularly considering that only 18% of patients with a prior fracture were prescribed a bisphosphonate, a group that benefit most from any treatment, particularly bisphosphonates[209]. Alternatively, the apparent undertreatment may be due to time constraints and the fact that GPs only have very short consultations in which to address many and complex issues[532].

A previous study[493] has shown, that a multi-faceted approach, including an educational outreach visit, was useful at increasing the prescribing of anti-osteoporotic medications in people prescribed long-term corticosteroids. A similar intervention is probably needed for osteoporosis in general and in the usefulness of QUS machines in the detection of at-risk subjects.

In addition to educating physicians, it is important to educate patients. Even after receiving education from the pharmacist and then consulting their doctor, there were cases where subjects refused to accept their risk of osteoporosis. For example, one GP reported that all the "high-risk" patients he referred for DEXA testing refused, and others (with fractures) declined treatment with bisphosphonates. The reasons for this may be explained by patients' lack of awareness of their personal risk, but also other constraints such as lack of transport to access a DEXA machine. One lady commented that, "she will only travel to a large city if it's an emergency", while another (who refused treatment) said that, "the doctor didn't seem to know much and just said I should have some tablets". Furthermore, some patients may simply ignore their risk for osteoporosis and choose to do nothing, while others believe they are "too old" to benefit from treatment and that, "the whole service may be more beneficial if it was started on a younger age."

Although the patient satisfaction survey was carried out using a questionnaire that, as yet, has not been validated for use in any population, it appears to give some insight into the views and satisfaction of patients regarding osteoporosis screening in community pharmacies. Subjects were overwhelmingly positive following the screening, and this was demonstrated from the survey responses.

There were cases where subjects who were shown to be at high risk did not seek further advice or who did not, or, chose not to have further investigations or commence treatment. For example, one patient had a T-score of –2.7 (likely to be osteoporotic), had previously broken bones, yet did not consider herself at risk and informed the pharmacist that the only reason she had the test performed was because she was asked by an assistant if she would like it done, and thought "it would be a bit of fun". But perhaps her concern was related to the perception that she may lose her independence. During the follow-up telephone-call she spoke about the need for her to continue to assist on the family farm and because she needed to be active, she was not interested in seeking further help from her GP who may "make me stop what I'm doing".

A focus group-based study[533] on rural women with osteoporosis found women with osteoporosis living on farms, decreased their participation in social activities and that independence was an ongoing concern. Those living on farms said they faced the additional challenge of avoiding the risk of falls while continuing to do physical labour necessary to maintain their rural lifestyle.

It has been shown that women often do not perceive a personal susceptibility to osteoporosis and only women actively worrying about developing osteoporosis are more likely to be engaged in significant osteoporosis behaviours[534]. Fiandt *et al*[535] also found that older (age greater than 65 years) rural women underestimated their risk for a number of diseases, including osteoporosis, and that life experience has more influence

on risk perception than the presence of actual risk factors. It may be possible that the opinion "you can't prevent everything anyway" identified in a previous qualitative study of younger women[536], increases with age.

However, some subjects often illustrated an insightful awareness of the seriousness of osteoporosis and the value a community pharmacy can provide, as demonstrated by one subject who stated:

> *"I feel there's further need for education and probably the pharmacy is a good place to start, as a number of people don't go to doctors until it is too late, but many go to the pharmacy for over the counter medicine"*

A study by Tellier *et al*[537] highlighted the importance of educating patients as well as physicians to increase awareness of osteoporosis. They evaluated a 15-year health promotion for osteoporosis. The medical community and general population in one city (intervention) in Belgium received constant health promotion aimed at postmenopausal women. The other city was a control and received no promotion. Self-reporting of osteoporosis was higher in the intervention than control (11% v 5%), as was prescription use of drugs for osteoporosis (26% v 10.5%). The demographics of the two cities were similar.

Direct to consumer advertising (DTC) could lead to important health benefits if patients seek and obtain appropriate care at an earlier stage, and thus avoid disease complications and admissions to hospital[538, 539]. However, evidence to support these claims is weak or absent[540]. Weissman *et al*[541] claimed that DTC advertising leads to important new diagnoses, however, this has been criticised because the survey lacked a control group[542]. There is no evidence that DTC advertising provides patients with the

correct medication. Perhaps patients would benefit more from advertising informing them of the risks and complications from osteoporosis, and advising them to discuss this with their doctor.

A study investigating DTC marketing of osteoporosis drugs has shown that it may increase health services utilisation such as bone density testing[543]. Another study found DTC advertising in one region had a higher self-report of seeing advertisements for various medications (including raloxifene) than in a region without DTC advertising. In addition, the subjects in the DTC region also reported requesting advertised drugs from their doctor. There is ample evidence that DTC marketing has increased consumer awareness of advertised prescription products[540] and that this has affected consumer behaviour and physician prescribing practices[544]. It remains controversial whether or not DTC can affect patient outcomes, such as reducing the burden of osteoporosis to society.

There has been very little research published on the role pharmacists have in the screening of osteoporosis[481]. Certainly, pharmacists are in an ideal position to advise and counsel patients prescribed long-term corticosteorids[493] on the risk and methods to reduce risk of osteoporosis while treated with corticosteroids. Elliott *et al*[481] found that screening rural elderly American women with a calcaneal DEXA scanner in community pharmacies led to women seeking medical advice and subsequent central DEXA scanning and commencement of medication. There have been papers written that encourage pharmacists to engage in osteoporosis screening programmees[428, 545]. In a study of women aged over 25 years and given a heel BMD test and counselling in a pharmacy, approximately two-thirds of women stated they would commence a calcium supplement and the majority (90%) reporting their knowledge had increased. However, longer-follow-up data were not available[546].

Today's health-conscious society has more readily accepted pharmacists in the role of patient educator and often actively seeks information from them. The reason why there is little information on pharmacists being more actively involved in patient education in osteoporosis is related to many factors. First, the medical profession has only recently begun to direct its attention to the prevention of chronic diseases and pharmacist involvement in the health care system usually begins only after diagnosis of a particular disease and the initiation of therapy. Secondly, pharmacists may not perceive themselves as being adequately informed to undertake the role of patient educator in the area of osteoporosis, although the results of a survey in the United States does not support this[547]. This survey was undertaken in 1988 and may not be reflective of current practice given the change in pharmacy graduates' education and clinical training.

There is certainly scope for further research on the role pharmacists have in educating patients on the prevention and treatment of osteoporosis. This is important considering 21% of subjects consulted their usual pharmacist following the screening. This also highlights that pharmacists are held in high regard by the public[426, 428]. Pharmacists must learn to take the initiative in providing information to their patients. There is evidence that demonstrates the overwhelming importance of the GP and pharmacist in provision of preventive health information for all rural people[548].

The pharmacist satisfaction survey demonstrated pharmacists were definitely positive regarding the screening in community pharmacies. For example, one pharmacist stated, "there should be more of this type of preventive approach and chronic disease management implemented in community pharmacies", while another said that the screening was "very useful but the combination of extensive counselling (diet and lifestyle modification) dramatically increased patient satisfaction and improved health

outcomes". However, one pharmacist did comment that it was too thorough – "osteoporosis screening/patient education etc when done as professionally and thoroughly as this programme would be far too time consuming for the average pharmacy/ist to conduct". Perhaps pharmacy assistants could be trained to administer the questionnaires and perform part of the screening and allow the pharmacist to counsel on the possible need for medications (e.g., calcium supplements) and further follow-up by their GP.

In Australia, community pharmacies often allow QUS screening to be performed by private companies, although screening of unselected populations is not recommended by any authoritative group in the field of bone biology[209]. This study screened a population that were at higher risk and those that had not reported previous BMD testing. The study aligned itself with recommendations from the US Preventive Services Task Force that recommends women over 65 years undergo routine screening for osteoporosis[471]. Black also concluded that there was ample justification for screening and treating elderly women[472]. In addition, the study also complied with the position statement on the use of QUS in the management of osteoporosis issued from the United Kingdom's National Osteoporosis Society[443].

This study found that if a nationwide screening on all women over the age of 65 years was implemented then it is unlikely to show a cost-benefit. This most likely reason for this is the relatively high cost of drug therapy. The cost of screening and treating far outweigh the benefit under the current PBS costing arrangements. We found that screening women over 65 years would show a cost-benefit (saving $840,000 per annum) provided the price of bisphosphonate therapy is reduced from $60 to $40 per month and the subjects made a contribution to the screening test ($20).

There are limitations to our cost analysis. We assumed that the women who received treatment were at highest risk and would account for only 66% of the costs associated with fractures. However, this figure is likely to be higher and therefore underestimating the cost-benefit of our screening programme. We have also assumed that all women over 65 years of age are screened and clearly this is unlikely to occur given that some of these women already are treated or have been diagnosed with osteoporosis. Again this assumption is likely to underestimate the savings. Unfortunately, little data exist on what proportion of woman over 65 years of age have been diagnosed or treated for osteoporosis in Australia. The NHANES III study[549] found that approximately 7% of women were aware they had osteoporosis and this is likely to be the same in Australia based on the Geelong Osteoporosis Study[289] (Sam Korn, personal communication). Finally, and possibly most importantly, we have only accounted for the direct cost of fractures alone, and have ignored other costs associated with osteoporosis, such pain, GP visit costs, further investigation costs (e.g., DEXA), carer costs, and rehabilitation (e.g., physiotherapy) costs. It is thus likely that the additional savings made from these costs will then negate the cost of screening and treatment.

Other authors have suggested that QUS may be a cost-effective alternative in routine pre-screening, especially where the availability of DEXA and resources is limited[550-552]. Recently, a Spanish cost-effectiveness study of QUS found that incorporation of QUS as a screening tool for osteoporosis in women over 65 years or older provides a slightly improved referral procedure to that currently achieved by DEXA alone in terms of the cost per osteoporosis case correctly detected. They suggested that QUS might be used as a selective pre-screen for DEXA but only in a complementary rather than an alternate way. The screening strategy with QUS may be

an option in those circumstances where the diagnosis of osteoporosis is deficient because of the difficulty in accessing DEXA equipment. It has been estimated that only 25% of postmenopausal women have access to BMD assessment in the United States[553] and this is likely to be similar in Australia. This scenario will radically change once the diagnostic potential of QUS is fully validated in currently ongoing prospective clinical studies that will clarify the correlation of QUS parameters with fracture risk independent of BMD measured with DEXA[554].

Hans *et al*[437] used two different QUS devices on a large Swiss population and proposed guidelines that would mean DEXA scans would not be required for those patients identified as having a very high risk of osteoporosis by QUS. Hans stated that approximately 48% of DEXA scans could be avoided and furthermore, it was suggested to be cost-effective. These proposed guidelines are shown in Figure 28. A clinical routine validation is currently underway to check this approach, and a cost-effective analysis is also planned. The approach proposed differs from the one we used as it is not designed as a general screening strategy but such that QUS can be used as part of a diagnostic approach, and reduce the need for expensive DEXA testing.

There are other limitations to our study. The vast majority of women were self-selected volunteers and might not be representative of rural elderly women. In observational studies there are concerns about the healthy volunteer effect[555]. It is possible that the women in this study were healthier and more motivated than the general population. However, it is worth noting that only 12% of subjects who underwent screening were HRT users, and the majority of women had an inadequate calcium intake (with only 16% taking calcium supplements and 10% taking vitamin D supplements when the screening was performed) and therefore perhaps no more interested in osteoporosis than the general population. Furthermore, many of the patients

taking vitamin D supplements were taking it in the form of cod liver oil and were not taking it for bone protection, rather treatment for other conditions such as arthritis.

It is also worth noting that the women in this study were taking a median of 4 medications with 51% taking 4 or more medications. Australian data from 1995[556] established that approximately 19% of patients 65-74 years and 33% of patients 75-84 years consume four or more medications. This suggests that perhaps the patients presenting to the screening were no more likely to suffer conditions requiring medications than the general population and hence the "worried well" were not the majority participating in the screening. It may also partially explain why few women commenced medications such as the bisphosphonates following the screening.

Another limitation of this study is the reliance of subject self-reporting previous fracture after the age of 50 years. It is likely that we may under-report the number of fractures, considering the median age of our subjects was 71 years. A study by Honkanen *et al*[557] found that self-reporting of fractures is a relatively accurate way to obtain information about past major fractures in perimenopausal women. However, it was rather insensitive in the detection of minor fractures, if the reporting period was several years. Hence it is likely that given our older cohort, there was under-reporting of minor fractures. Likewise, Ismail *et al*[558] found that self-reporting was a relatively accurate method for obtaining information about the occurrence of hip and distal forearm fractures, including their timing. Accuracy of ascertainment of fractures at other sites was less accurate and where possible self-reported fractures at such sites should be verified from other sources. Interestingly, women were likely to be more accurate than men ($p = 0.04$).

Short-term outcomes further limit our conclusions and any long-term outcomes are largely unknown. In our follow-up, approximately one-third commenced a

medication, however it is well known that a proportion of these will stop their therapy. A study of 956 women who were interviewed on average 7-months after treatment found that 26% had discontinued HRT, 20% had discontinued raloxifene and 19% had discontinued alendronate. Women were more likely to discontinue therapy if they reported bothersome side effects, or thought that their bone density test results did not show osteoporosis[482]. Another recent study also revealed women often displayed less than optimal adherence to antiresoptive treatment and often discontinued their therapy for osteoporosis[483]. It is known that one woman in this study discontinued alendronate due to intolerance and thought she was "going to die", while another reported discontinuing calcium due to constipation and another thought it was linked to depression.

It is also important to consider that in this study a single pharmacist conducted the screenings and it (the study) did not test the feasibility of the community pharmacist themselves offering the screening, rather it studied the feasibility of the community pharmacists themselves hosting screening. In addition, there are also implementation issues to consider if pharmacists are going to introduce screenings in their pharmacy. To be sustainable in the long-term, pharmacists would need to be remunerated either directly from the patient or through government subsidies. Pharmacists may also find the initial aquasition cost of the QUS machine (approximately Aust $30,000) prohibits them from purchasing one. However, a group of pharmacists could collectively purchase the machine and share the cost. The follow-up surveys did not assess whether the participating pharmacists would be willing to perform the testing themselves or identify barriers to implementation of osteoporosis screening if they conducted it themselves. A possible barrier for community pharmacists to implement osteoporosis screening in their pharmacy is the time required to receive training to use the machine and time to

undertake screenings as well as perform their usual professional activites. Pharmacy assistants will need to be trained to undertake part of the screening process.

A final limitation was that simple self-report at follow-up was used to assess outcomes such as lifestyle changes and did not use an objective method to assess subjects' changes.

This study does have several strengths and adds substantially to the knowledge on the usefulness that community pharmacies possess. Firstly, the study utilised a previously validated method for categorising subjects as potentially osteoporotic and did not rely on the WHO classification. There have been studies that have indicated that the WHO criteria were not applicable to calcaneal QUS measurements[438, 476, 477]. This is due to important variations of T-score thresholds for the different QUS devices (depending upon the method used to determine the cut-off value and on the QUS technology)[436, 559, 560]. Presently there are different guidelines on how to use QUS in practice. We chose to use the Frost proposal[438, 479] as this was one of the first studies to demonstrate that when the WHO defined T-scores for osteoporosis were altered for three different QUS devices (including the Sahara), the same percentage of women would be identified as osteoporotic, osteopaenic or normal as central DEXA. Although QUS is not currently recommended to be used to diagnose osteoporosis, when Frost's classification was used in pre-screening testing, we found that only 2 of the 26 volunteers were incorrectly classified for osteoporosis, osteopaenia or normal compared to the WHO classification using DEXA. We therefore support the notion that QUS is useful for identifying those at risk and could be potentially used for diagnostic purposes as recently proposed by Hans *et al*[437].

Secondly, the very high response rate that was achieved from the postal survey and phone follow-up minimised the non-response bias[561]. In fact all 345 subjects

participating in the screening were contacted by phone and almost 90% returned postal surveys.

Prior to the commencement of the current study an attempt was made to validate Frost and colleagues'[438] classification for osteoporosis/osteopaenia/normal using the Sahara portable ultrasound machine. It was demonstrated that in a relatively small sample QUS is a useful method for identifying postmenopausal women at risk of osteoporosis. We achieved a high correlation (as demonstrated by high Kappa values) and statistical significance when Frost's classification was compared to the WHO classification for osteoporosis. Other studies[438, 562-566] have found much higher discordance when applying the WHO classification for osteoporosis to QUS. Frost *et al*[438] found that when they applied the WHO criteria to their sample of women aged over 50 years, only 3-4% would have been classified as osteoporotic compared to a mean of 15% identified on DEXA. Our results, although in only a small sample, demonstrated only 2 (8%) misclassifications.

One subject (number 10) who was misclassified was normal on DEXA and shown to be osteopaenic on QUS. It was noted that this subject had significant ankle oedema. Peripheral oedema has been previously reported to produce lower QUS readings than in those people without oedema[567]. Approximately 5% of subjects in the screening programme (n = 16) had mild peripheral oedema at time of testing and this was reported to their GP. The second subject (number 22) was shown to be osteopaenic on DEXA testing and osteoporotic on QUS testing.

The pre-screening sample QUS results had a better correlation to femoral neck T-score (r = 0.9) compared to lumbar spine T-score (r = 0.8). This is of particular importance as measurement of BMD at the hip is considered the "gold standard" in

terms of site, since it has the highest predictive value for hip fracture, which is the most severe complication of osteoporosis[205].

In summary, when the revised classification for osteoporosis was used, as proposed by Frost[438], unlike other studies[438, 562-566], QUS at the heel was extremely sensitive and specific for detecting osteoporotic and non-osteoporotic subjects. In addition the operator (MN) who performed the screening demonstrated similar precision to that published by Frost[568]. The operator showed precision of 2.6%, comparable to Frost's reported 3.3% and the manufacturer's precision specification of 3% for estimated BMD measurements[436].

This study also adds to the knowledge on the skeletal health of rural elderly women, a population that has not been extensively studied. In this study, approximately 20% of women (when using a revised WHO classification for osteoporosis as previously discussed) were shown to likely have osteoporosis and 46% would have likely to have been classified as osteopaenic at the hip or lumbar spine. This is comparable to the osteoporosis prevalence reported in Third National Health and Nutrition Examination Survey (NHANES III), a large probability sample of United States population. As assessed at the femoral neck, 20% of postmenopausal white women have osteoporosis[549]. Because osteoporosis is a systemic disease, data suggests that 54% of white postmenopausal women in the United States have osteopaenia and a further 30% have osteoporosis[569]. Our observation that 20% of women are likely to have osteoporosis, suggests that a significant number of rural elderly women may benefit from osteoporosis screening and increased availability appears reasonable, particularly as DEXA is limited in general[553], and even more so in the rural population[549, 570]. Similarly, Elliott *et al*[426] found that 20% of rural women in the United States who

presented for calcaneal DEXA screening in community pharmacies would be classified as osteoporotic.

Our cohort of subjects demonstrated a weak but significant age-related decline in estimated BMD T-score. The average T-score for women aged 65-74 was –0.6 (-2.9-1.9) compared to those women aged over 75, which was –1.2 (-3.0-1.8). Hans *et al*[437] stated that DEXA could potentially be omitted (i.e., use QUS results alone) in those aged over 75 years for whom monitoring is not crucial or for those treated with drugs which have an improved reduction on fracture risk than on increases in BMD (e.g., raloxifene). Our results also demonstrated that older women appear to have a significantly greater risk for fracture.

Almost one-half (46%) of our subjects had an estimated BMD T-score $\leq$ -1.0 which was similar to a previous study conducted in elderly rural Korean women[571]. Not surprisingly, women aged over 75 years had a significantly lower BUA Z-score, median = 0.2, compared to women aged 65-74 years, median = 0.9, ($p = 0.0008$). It has been previously shown that there is a decrease in BUA with increasing age[438]. The 5-year fracture risk in women aged over 75 years was therefore significantly higher, 14.9%, compared to the younger (65-74 years) subjects, who had a 5-year fracture risk of 5.6%.

There are unfortunately little data on the average BUA measurements in rural elderly women (Caucasian) and none in Australia using the Sahara ultrasound. However, the women in this study appeared to have a lower risk for fracture compared to the subjects used in Frost's study[438]. For example, the mean T-score was reported to be –1.1 in women aged 65 years, compared to –0.6 in the women (n = 37, aged 65 years) in this study. Hence, it is suggested that rural elderly women in Australia have higher QUS values than urban women, and therefore have a lower fracture risk. However, this will need to be confirmed in a larger QUS study comparing urban and rural populations

within the same region, since Frost's population was in the United Kingdom and were mostly referred by their GP for routine done density screening by DEXA or were from the general population who volunteered to participate in clinical research. Local published data has shown that rural women have a lower risk of fracture compared to their urban counterparts[219]. It is interesting to note that a recent community-based survey in Taiwan using QUS found that BUA values in urban subjects were *higher* (and therefore perhaps at lower risk) than rural-dwelling subjects[572].

As previously mentioned, calcaneal QUS bone measurements are correlated with measurements at axial sites, and have been shown to predict fracture risk[205, 425, 431, 444-466]. For example, the EPIDOS study of 5662 women (mean age 80 years) showed a 2-fold relative risk for hip fracture for a 1 SD reduction in BUA[425]. In an even more recent large prospective study using QUS, one standard deviation decline in BUA was associated with a relative risk of about 2.2 for hip and 2.0 for other fractures[452]. Subjects over 75 years were more likely to report a previous fragility fracture than women aged 65-74 years (27% v 17%; $p = 0.03$). This is consistent with literature reporting older subjects are more likely to sustain fragility fractures[221].

Chapter 5: Conclusion

The overall place of point of care testing using portable QUS devices has yet to be firmly established, in particularly in community pharmacies. Possible methodologies include point of care testing as a stand-alone test[455] (ideal for rural communities), as a prescreening for central DEXA testing[550, 551] or a composite approach using both QUS and DEXA measurements to assess risk[455].

This project has demonstrated that community pharmacies in rural areas can serve as a useful environment to conduct osteoporosis screening. Point of care testing may be considered an option to determine which patients need central DEXA testing or in more extreme circumstances when DEXA is not available, to initiate therapy. Alternatively, point of care testing with QUS may be used when the patient is first unwilling or financially unable to undergo DEXA testing. In addition, subjects undergoing osteoporosis screening discussed their results with their usual doctor and a significant number commenced medication to prevent or treat osteoporosis and/or make lifestyle changes following screening. Screening for osteoporosis was well received by rural women undergoing testing and pharmacists participating in the screening programme. General practitioners subjected to the screening, via their patients, acknowledged community pharmacists can assist doctors in the identification of women at risk and their patients found the screenings useful, but remained relatively uncommitted whether screening with QUS should become widespread. With increased education of GPs and pharmacists on QUS and clear guidelines from authorities in the field of bone biology, screening in community pharmacies for osteoporosis appears to be a promising additive service pharmacists can recommend to elderly patients.

Part II (b): Evaluation of a multi-faceted educational programme to increase prescribing of preventive medication against corticosteroid-induced osteoporosis

Chapter 1: Introduction

Background

Corticosteroids have extensive clinical uses[179]. They are used primarily for their anti-inflammatory and immunosuppressive effects in the treatment of many conditions including chronic obstructive airways disease, rheumatoid arthritis, ulcerative colitis and severe inflammatory conditions of the skin and eye, and in the treatment of some leukaemias and lymphomas[52].

While corticosteroids have many useful clinical applications, they also have a large profile of unwanted effects. These include: electrolyte disturbances, hyperglycaemia, muscle weakness, easy bruising, Cushing's syndrome, adrenal suppression, susceptibility to infection and masking the signs of infection[363]. Long-term use is associated with osteoporosis and an increased risk for fracture[573].

Corticosteroids are widely used in the community. A cross sectional study in England in over 65,000 patients (52% female) showed that 0.5% (1.4% of patients aged over 55 years) were taking "continuous" (> 3 months) oral corticosteroids. Prednisolone was the most commonly used corticosteroid (97%) and the mean dose was 8 mg/day of prednisolone, with a median duration of treatment of three years. The main indications for oral corticosteroids were rheumatoid arthritis, polymyalgia, and asthma or chronic obstructive pulmonary disease. Only 14% of patients of the patients had received treatment for the prevention of osteoporosis over the past four years. If these figures are typical then they suggest that over 250,000 people in the United Kingdom are taking continuous oral corticosteroids and that most of these are taking no prophylaxis against osteoporosis[574].

The adverse effects of hypercortisolism on bone were recognised more than half a century ago[187] but today, the iatrogenic form of the disease has become far more common than Cushing's syndrome and corticosteroid-induced osteoporosis is probably the most common secondary type of osteoporosis[575]. It is estimated that as many as 50% of patients requiring long-term corticosteroids for control of rheumatologic, pulmonary, or gastrointestinal disease, or to prevent transplant rejection will ultimately suffer fractures[575, 576].

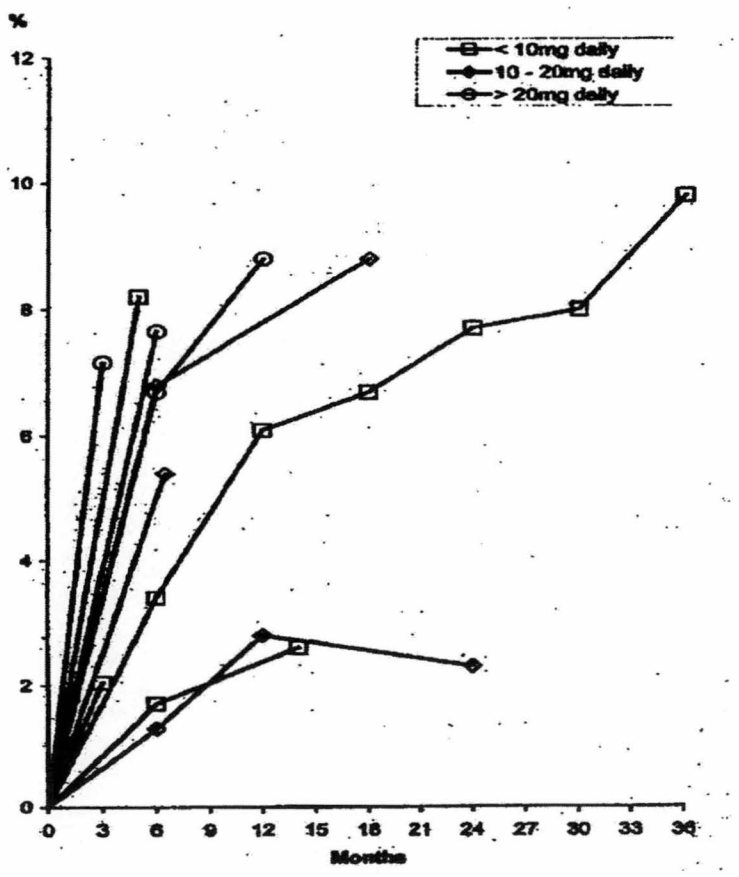
Epidemiology

Oral corticosteroid use and BMD

In postmenopausal women, a decrease of 1 SD in BMD is associated with a doubling in fracture risk[214]. This relationship may be an underestimate in patients treated with corticosteroids, who appear to suffer fractures at bone density values higher than in

postmenopausal osteoporosis[577]. Van Staa *et al*[573] recently performed a comprehensive meta-analysis on corticosteroid-induced osteoporosis and found lumbar spine and hip BMD measurements of corticosteroid users were consistently lower than expected for a group of similar age and sex. Spinal BMD was on average 89.4% of that expected (2305 users, 50 studies). For the hip, this figure was 88.8% (1955 users, 37 studies). The distal radius was 88.3% of the expected values (591 users, 15 studies). Figure 37 shows the bone loss from the spine of first-time users who were followed in longitudinal studies. It must be noted that a limitation when evaluating bone loss longitudinally is that daily dose may vary and reduce over time[573].

Figure 37 Loss of spine BMD after start of corticosteroid therapy in ten longitudinal studies[573]



Van Staa also identified a strong correlation between cumulative corticosteroid dose and decreases in spine and hip BMD, so much so that when any study was excluded from the analysis the associations persisted[573]. It has been widely debated in the literature whether there is a dose threshold for the adverse bone effects of corticosteroid therapy. Van Staa identified studies using daily doses on average of 7.5 mg prednisolone or less at the time of BMD measurement and found conflicting results. Several studies found substantial reductions in BMD at lower doses, in contrast to others[578]. Many of the studies identified by van Staa were difficult to interpret as the daily dose used prior to BMD measurement were frequently unknown and not taken into account. The most convincing information on the effects from low doses of corticosteroids come from two randomised clinical trials which found statistically significant reductions in BMD in patients using daily doses of 7.5 mg prednisolone with an 8.2% loss spine BMD at 20 weeks in one study[579]and 2% at 12 weeks in another[580].

The rapid onset of bone loss occurs within the first months of starting corticosteroid therapy, slowing down after about one year of therapy (Figure 37)[573]. Whether the increased risks of bone loss and fracture with corticosteroid use persist following discontinuation of therapy is also important to consider. There is solid evidence that suggests corticosteroid-induced osteoporosis and its consequences are readily reversible after corticosteroid therapy is ceased. Longitudinal studies have shown substantial increases in BMD after discontinuation of corticosteroid therapy[579, 581] and two cross-sectional studies found that BMD of past corticosteroid users was comparable to that of non-users[573]. Similarly, substantial increases in BMD have been reported after cure of Cushing's syndrome[582].

The effect of corticosteroids on BMD has not been completely established as it is known that systemic disease processes can also contribute to loss of bone density,

independently of corticosteroid therapy[583]. In van Staa's meta-analysis, it was suggested that a substantial loss of BMD is related to corticosteroid therapy[573] and overall the effects of cumulative dose on BMD were not influenced by age or sex[573]. With respect to underlying disease, two studies have reported no differences in the effects of corticosteroids on BMD in patients with rheumatic or lung disease[584, 585].

Use of oral corticosteroids and risk of fractures

A plethora of literature exists detailing the deleterious effects of corticosteroids on BMD[573]. While this relationship is important and decreased BMD can predispose patients to be at increased risk for fracture, other studies in various populations have shown an increased risk for fractures in corticosteroid users with minimal or no change in BMD, which implies that corticosteroids may have a direct effect on the quality of bone that leads to an increased risk for fracture[573, 586-588]. For example, Peel *et al*[588] found that there was a 6-fold increase in the risk of vertebral deformity in corticosteroid users compared to controls, but with only a 0.8 SD reduction in lumbar spine BMD. Further evidence can be found when comparisons are made between placebo groups from clinical trials with regard to fracture rates and BMD. There is a much higher incidence of vertebral fractures in patients with corticosteroid-induced osteoporosis compared to those with postmenopausal women osteoporosis, despite a higher BMD at baseline in patients with corticosteroid-induced osteoporosis. This strongly indicates that the risk of fracture may be substantially higher in corticosteroid-induced osteoporosis at a similar level of BMD compared to senile osteoporosis[589].

It has been of interest to see if patient characteristics such as age, sex or underlying disease predispose to fracture as not all patients on corticosteroids develop

fractures. Van Staa *et al*[590] found that the relative risk of fracture with corticosteroid therapy was similar for age, sex and underlying disease. For example, the risk of hip fractures was increased in female users by 59% and by 67% in male users of corticosteroids. Also, patients with obstructive pulmonary disease showed comparable increases in risk of fracture compared to patients with arthropathies[590]. There have been studies with conflicting results on individual susceptibility to fractures. For example, Naganathan *et al*[587] observed a higher increase in vertebral deformities in older users of corticosteroids whereas Peel *et al*[588] observed the converse.

A study by Cooper *et al*[583] found that using corticosteroids doubled the risk of developing hip fracture. However, after adjustment for confounding variables, the increased relative risk was insignificant. There have been other studies that have identified an increased risk of fracture when treated with corticosteroids[578]. None of these studies provided evidence of the relationship between dose and reversibility of fracture risk after cessation of therapy.

The largest study investigating the relationship between corticosteroids and fractures was conducted by van Staa *et al*[578] in the United Kingdom. This retrospective study {referred to as the General Practice Research Database (GPRD) study} was conducted in a general practice setting comprising of 244,235 oral corticosteroid users and 244,235 matched controls. The average age was 57 years in both the oral corticosteroid cohort and the control cohort. In both cohorts 59% were female. The most frequent indication for treatment was respiratory disease (40%). The relative rate of fracture during oral corticosteroid treatment was 1.33 (95% confidence interval, 1.29-1.38) for nonvertebral fracture, 1.61 (1.47-1.76) for hip fracture, 1.09 (1.01-1.17) for forearm fracture, and 2.60 (2.31-2.92) for vertebral fracture. A dose dependence of fracture risk was observed (Table 53).

Excess fracture risk in corticosteroid users was stable at about 20% for daily doses below 5 mg prednisolone but increased for higher doses. Patients who had used a daily dose of 20 mg had a nonvertebral fracture rate, which was approximately 60% higher than the rate in the control group[591]. Cumulative corticosteroid dose was also correlated to the risk of fracture, but this correlation was weaker than that observed between daily dose and risk of fracture. Positive correlations between cumulative dose and fracture risk were also found in other studies[592, 593]. The dose dependence of corticosteroid-induced fractures and the increased risk of vertebral fractures, even for doses between 2.5 and 7.5 mg/day, indicates that there is no 'safe dose' of oral corticosteroids[591].

Table 53 Fracture risk according to dose of oral corticosteroid (low < 2.5 mg/day, medium 2.5-7.5 mg/day, high ≥ 7.5 mg/day)[578]

	Low dose Adjusted relative rate (95% CI)	**Medium dose** Adjusted relative rate (95% CI)	**High dose** Adjusted relative rate (95% CI)
Nonvertebral	1.17 (1.10-1.25)	1.36 (1.28-1.43)	1.64 (1.54-1.76)
Forearm	1.10 (9.96-1.25)	1.04 (0.93-1.17)	1.19 (1.02-1.39)
Hip	0.99 (0.82-1.20)	1.77 (1.55-2.02)	2.27 (1.94-2.66)
Vertebral	1.55 (1.20-2.01)	2.59 (2.16-3.10)	5.18 (4.25-6.31)

With a standardised daily dose of less than 2.5 mg prednisolone, hip fracture risk was 0.99 (0.82-1.20) relative to control, rising to 1.77 at daily doses of 2.5-7.5 mg, and 2.27 at doses of 7.5 mg or greater. The annualised incidence of hip fracture stratified by daily dose is shown in Figure 38. For vertebral fracture, the relative rates were 1.55, 2.59, and 5.18, respectively. All fracture risks declined toward baseline rapidly after cessation of oral corticosteroid treatment (Figure 39), which further establishes the

independent effect of corticosteroid exposure on fracture risk. The highest number of fractures occurred among females using daily doses of 7.5 mg or more. The study also demonstrated that the increase risk for fracture occurs within the first three months of treatment. In patients using 7.5 mg or more of prednisolone per day, the risk of nonvertebral fractures was increased by 54% in the first year of therapy compared to baseline. In patients with continued corticosteroid therapy, the rate of fracture did not change substantially. The risk of vertebral fractures also increased greatly in the high dose group[578]. Interestingly, two studies found no difference in risk of vertebral fractures between new and long-term corticosteroid users[594, 595].

Figure 38 Annual incidence of hip fractures stratified by daily dose of corticosteroid (● high dose, ■ medium dose, ▲ low dose, □ control) age and gender[596]

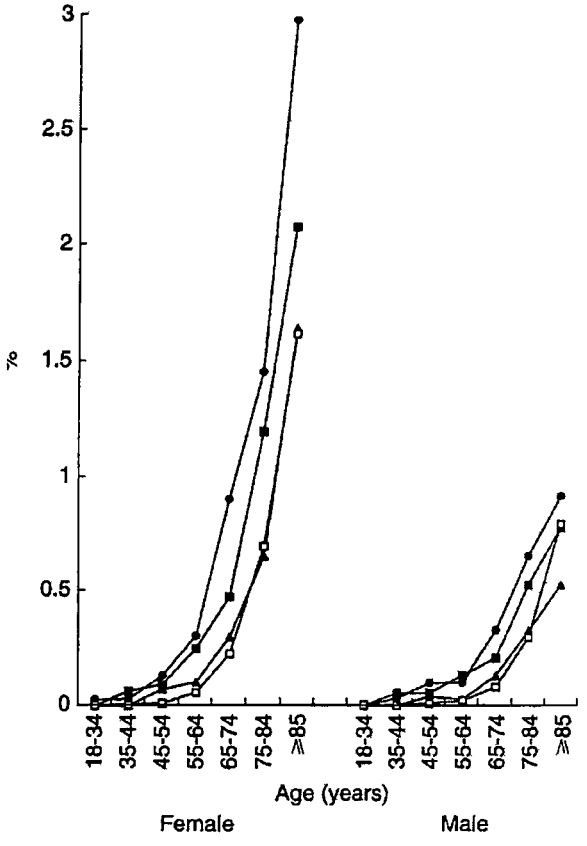
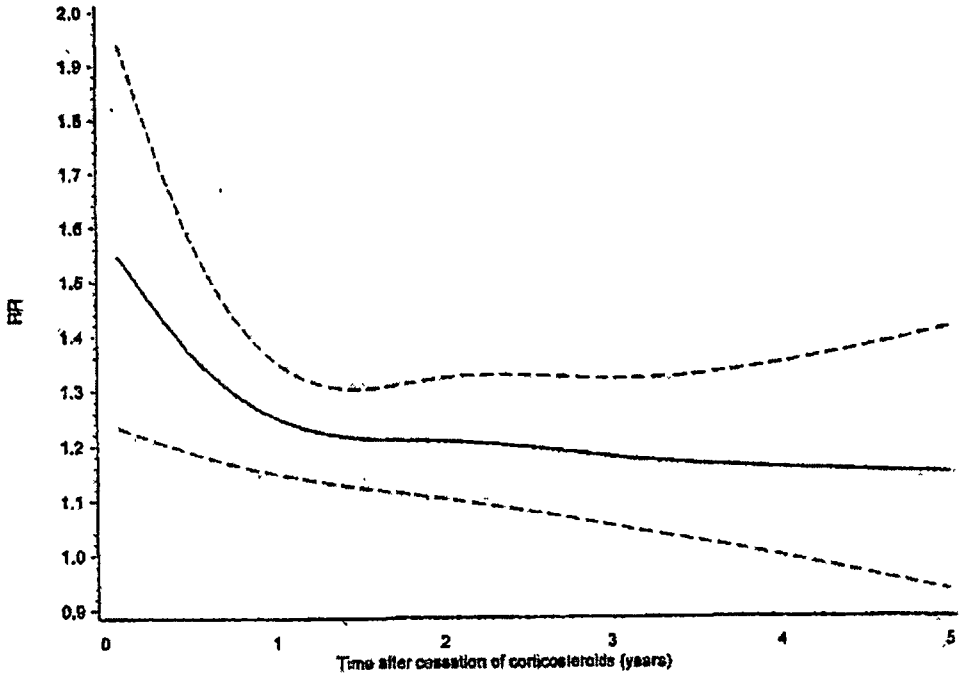


Figure 39 Adjusted relative rate (and 95% CI) of nonvertebral fracture after discontinuation of oral corticosteroids[578]



In van Staa's recent comprehensive meta-analysis on corticosteroid-induced osteoporosis, almost all of the studies (66 studies included in review) reported higher rates of fractures in corticosteroid users, although this increase did not always reach statistical significance in smaller studies[573]. Another recent large retrospective study of corticosteroid users corroborated van Staa's findings, demonstrating a 73% increased risk of hip fracture and a 173% increased risk of vertebral fracture in patients taking less than 10 mg/day of corticosteroid compared to non-users[597].

Van Staa *et al*[578] concluded that the risk of fracture appears shortly after the start of therapy and often at low daily doses, with an increase in risk observed with doses above 5mg/day. The risk of fractures is reversible after discontinuation of therapy. In the GPRD study, most of the excess risk of fracture disappeared within 1 year of stopping therapy and the decline was most pronounced for vertebral fractures[573]. A small study

also reported comparable rates of vertebral fracture in past users and controls[598]. Van Staa suggested that high-risk patients may include those over 65 years or older, or those with a low baseline BMD or fracture history.

Use of inhaled corticosteroids and risk of fracture

The potential effects of inhaled corticosteroids on bone are of great importance in view of their common use and often long exposure. Inhaled formulations should be used in preference to oral formulations when possible, to reduce the risk of systemic adverse effects. Nevertheless, it should be recognised that adverse skeletal effects may occur in individuals using inhaled corticosteroids, particularly when high doses are administered long-term[599-601]. The skeletal effects of inhaled corticosteroids appear to depend on both the dose and duration of use. There may be also differences between different forms of inhaled corticosteroids and there is some evidence that beclomethasone may have a more marked effect than budesonide or fluticasone because of greater systemic absorption[602].

Several cross sectional studies have examined the relationship between dose of inhaled corticosteroid and BMD with conflicting results. Doses above 800 mcg/day of beclomethasone dipropionate (BDP) or equivalent have been reported to result in decreases in BMD in adults[600], although this finding has not been universal[603, 604]. Wong *et al*[601] extrapolated their results from a prospective study in a group of young (aged 20-40 years) patients with only limited exposure to oral corticosteroids and found that the BMD in patients who would have taken 2000 mcg/day of inhaled corticosteroids for 7 years will be on average, one SD below the predicted value. In another large prospective study, BMD was measured in patients with mild asthma over a two year period[605].

Changes in BMD were small and there was no difference between users and non-users of inhaled corticosteroids. However, the control group had a higher exposure to oral corticosteroids and the treatment group used low doses of inhaled corticosteroid – budesonide 389 mcg/day and beclomethasone 499 mcg/day.

In a three year prospective study, significant bone loss in the proximal femur was reported in a group of premenopausal women treated for asthma with inhaled triamcinolone[606]. Furthermore, two other prospective studies[607, 608] of inhaled corticosteroids in chronic obstructive pulmonary disease have recently been reported. The Lung Health Research Group[607] reported that patients treated with inhaled triamcinolone showed greater bone loss than those in the placebo group, whilst in the EUROSCOP study[608] no bone loss was observed in patients treated with inhaled budesonide 800 mcg/day or in those taking the placebo.

A recent retrospective cohort study was conducted using the large GPRD in the United Kingdom of 170,818 inhaled corticosteroid users, 108,786 bronchodilator users, and 170,818 control patients and found that users of inhaled corticosteroids had an increased risk for fractures, particularly at the hip and spine. However, this excess risk may be related more to the underlying disease being treated than to the inhaled corticosteroid as patients using inhaled bronchodilators also had an increased risk for fracture[609]. The increase in relative rate of fracture observed was small for nonvertebral (15%), forearm (13%), hip (22%) and vertebral (51%) fractures. A statistically significant increase in hip (77%) and vertebral (150%) fractures was only observed at doses of beclomethasone greater than 700mcg/day. Cessation of therapy was associated with partial reduction in excess risk of fracture.

Another more recent population-based case-control study within a cohort of elderly patients (mean age 81 years) dispensed respiratory medications found the use of

inhaled and nasal corticosteroids was not associated with a significantly increased risk of fracture of the hip or upper extremities in elderly patients with respiratory disease, when used at the usual recommended doses over a 4 year period[610].

Richy *et al*[611] performed an exhaustive systematic research of all controlled trials potentially containing pertinent data, peer-reviewed by a dedicated WHO expert group, and comprehensive meta-analyses of the data. The authors reviewed twenty-three trials; 11 papers subsequently met inclusion criteria and were assessed for the main analysis. In their meta-analyses, budesonide at a mean daily dose (SD) of 686 mcg/day (158 mcg/day), beclomethasone at 703 mcg/day (123 mcg/day) and triamcinolone at 1000 mcg/day (282 mcg/day) were found to affect BMD and markers in patients suffering from the two major respiratory diseases.

Another large study utilising the GPRD to perform a case-control analysis, including 16,341 cases of hip fracture (mean age of 79 years, 79% female, median period prescribing data 2.7 years) and 29,889 control subjects, individually matched by age, sex, and general practice, was also recently published. Data for all prescriptions for corticosteroids and for potential confounders, including other drug use and comorbid illnesses, were extracted, and the impact of inhaled corticosteroid exposure was analysed using conditional logistic regression. The risk of hip fracture was associated with exposure to inhaled corticosteroids with an odds ratio of 1.26 (95% confidence interval, 1.17 to 1.36). This odds ratio was reduced after adjusting the model for annual courses of oral corticosteroids, the only confounder of note (OR 1.19; 95% CI, 1.10 to 1.28). There was a dose-response relationship between inhaled corticosteroid use and hip fracture even after adjusting for the annual number of courses of oral corticosteroids ($p = 0.007$). The authors concluded that in older subjects, the recent use of inhaled corticosteroids is associated with a dose-related increase in hip fracture[612].

In summary, the use of low-dose inhaled corticosteroids may be safe enough not to require special assessment of bone loss or the use of preventive measures. However, evidence is lacking on the risks of long-term use of higher doses. Regardless of dose, all patients given long-term systemic corticosteroids should be carefully examined and, if necessary, treated for bone loss[613].

Pathophysiology

Corticosteroids are known to affect bone through multiple pathways influencing both bone formation and bone resorption[614]. The systemic effects of corticosteroids, which indirectly affect calcium homeostasis and bone metabolism, are summarised in Table 54. Patients receiving prolonged corticosteroid therapy may develop hypogonadism due to inhibition of secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary gland, as well as direct effects on hormone production by the ovaries and testes.

Table 54 Systemic effects of corticosteroids which indirectly affect bone[615]

1. Defect in Calcium Transport
    - A. Impaired gastrointestinal absorption
    - B. Decreased renal tubular reabsorption
    - C. Defective transport into parathyroid cell
2. Secondary hyperparathyroidism
3. Deficiency of anabolic hormones
    - A. Diminished secretion of gonadal hormones
        - (i) Impaired secretion of gonadotrophins
        - (ii) Decreased secretion of oestradiol and precursors, and testosterone by ovary and testis
    - B. Decreased adrenal secretion of oestradiol, androstenedione, and DHEA due to suppression of ACTH
    - C. Decreased response to growth hormone and growth factors and changes in concentrations of IGF-binding proteins

Note. DHEA, dehydroepiandrosterone; ACTH, adrenocorticotropic hormone; IGF, insulin-like growth factor.

Effect of corticosteroids on bone metabolism

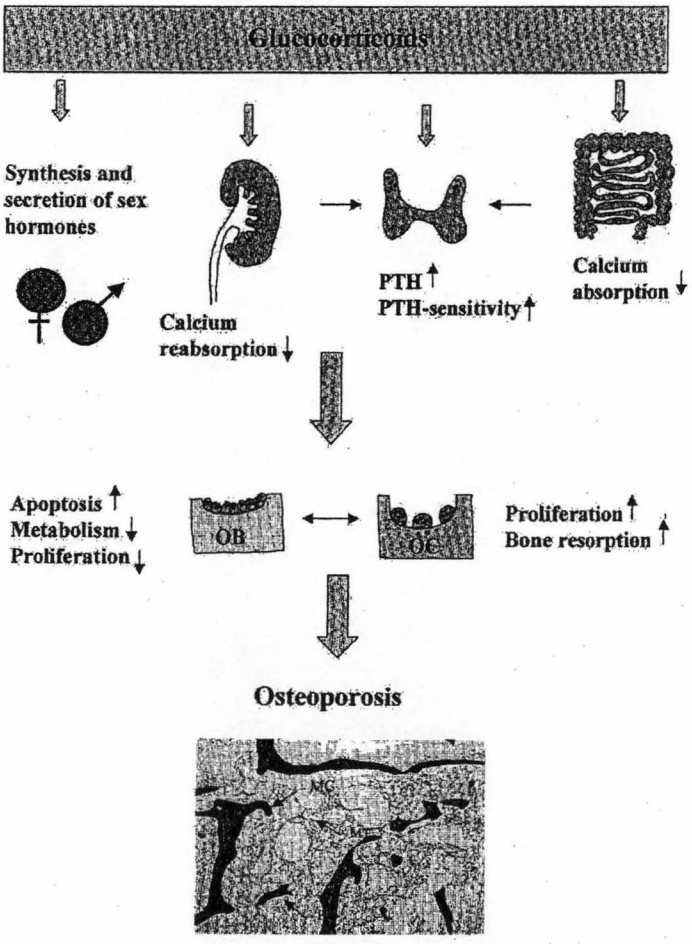
Corticosteroids have a significant impact on bone cells, and continued exposure of skeletal tissue results in increased bone fragility and osteoporosis[616]. From a clinical point of view, most bone loss occurs during the initial periods of exposure to corticosteroids, often during exposure to moderate doses often seen in the physiological replacement range[578]. Histomorphometric analysis of bone biopsies from patients receiving corticosteroids reveals increased bone resorption and decreased bone formation. However, the predominant finding is increased bone resorption. Although the pathogenesis of corticosteroid mediated bone loss is not completely understood, corticosteroids have a significant impact on the function of osteoblasts and osteoclasts[617, 618]. Figure 40 displays an algorithm of bone loss due to corticosteroids.

Bone formation

The major changes in corticosteroid-induced osteoporosis are a decrease in osteoblast activity that results in decreased matrix synthesis and a decreased active life span of osteoblasts. Corticosteroids decrease the number of bone forming cells by decreasing cell replication and by preventing the terminal differentiation of cells into mature functioning osteoblasts[619]. In addition, corticosteroids enhance the programmed cell death or apoptosis of mature osteoblasts, which results in a reduction of bone forming cells. Corticosteroids also alter the function of the osteoblast, inhibiting the synthesis of type I collagen, the major component of bone extracellular matrix, with a consequent decrease in bone matrix available for mineralisation[618].

The decrease in bone formation with corticosteroids has also been observed using biochemical markers of bone turnover, particularly osteocalcin, which decreases in a dose-dependent way within 4 days of starting corticosteroid treatment[620]. Another detailed study of serum and urinary markers of bone metabolism in patients with multiple sclerosis found that within 3 days of corticosteroid administration, 1,25-dihydroxyvitamin D and urinary phosphate clearance increased significantly, whilst serum phosphorus and serum osteocalcin decreased significantly[621]. These changes indicate that high-dose corticosteroids causes primary depression of bone formation as well as having direct effects on the kidneys. The decrease in bone formation results in a decrease in the mean wall thickness of trabecular bone[622].

Figure 40 Corticosteroid-induced bone loss mechanisms[623]



Bone resorption

Another major effect of corticosteroids is to decrease the intestinal absorption of calcium[614]. Corticosteroids also increase urinary phosphate and calcium loss by a direct effect on the kidney, which together with impaired calcium absorption, leads to secondary hyperparathyroidism and increased resorption. Although corticosteroids decrease calcium absorption in the gastrointestinal system, the increased bone resorption after exposure to corticosteroids cannot be explained by the secondary hyperparathyroidism. The serum levels of PTH in patients exposed to corticosteroids are not in the hyperparathyroid range. More importantly, patients exposed to corticosteroids develop a bone disease fundamentally characterised by decreased bone remodelling, whereas increased remodelling is found in hyperparathyroidism[617].

Possible mechanisms for modest increases in bone resorption in corticosteroid-induced osteoporosis include a decreased gonadotropin production, which may result in increased bone resorption due to oestrogen deficiency. In an oestrogen deficient state, increased levels of tumour necrosis factor (TNF)-α secreted by T cells play a central role in bone resorption, but it is not known whether elevated TNF- α levels are responsible for the enhanced bone resorption in patients with hypogonadism due to excess corticoid[618]. The increased bone resorption found in corticosteroid-induced osteoporosis appears to involve the receptor activator of NF-κB ligand (RANK-L) and osteoprotegerin. RANK-L is an osteoblastic signal that binds to an osteoclast receptor and in association with colony stimulating factor (CSF)-1, induces osteoclastogenesis. Osteoprotegerin is a decoy receptor that binds RANK-L preventing RANK-L binding to the osteoclast receptor, and subsequent osteoclastogenesis. Corticosteroids increase the expression of RANK-L and CSF-1 and decrease osteoprotegerin expression by human osteoblastic and stromal cells in culture. These actions result in increased

osteoclastogenesis and increased bone resorption, although patients exposed to corticosteroids eventually develop a state of decreased bone remodelling. This is because of their inhibitory effect on osteoblastogenesis, which results in decreased osteoclastogenesis[618]. Another reason for the eventual decrease in bone resorption and remodelling is an increase in corticosteroid -induced osteoclastic apoptosis[624].

Other factors may play a role in the development osteoporosis. Sex steroids are important determinants of bone turnover, and corticosteroid therapy may result in a dose dependent decrease in serum testosterone, although this may not have a direct effect[625]. The decrease in testosterone may be due to an alteration in hypothalamic gonadotrophin-releasing hormone secretion[626]. Corticosteroids may also have a direct effect on the production of testosterone by the testes[627]. In postmenopausal women, the major source of androgens and oestrogens are the adrenal glands, and adrenal suppression that results from corticosteroid therapy decreases the production of androstenedione, testosterone and oestrone[628]. Corticosteroids can also inhibit follicle-stimulating hormone that results in a decrease in oestrogen secretion in premenopausal women[629].

Skeletal growth factors

In addition to the direct actions of corticosteroids on bone forming cells, some of their effects on osteoblasts are to an extent indirect and mediated by changes in the synthesis, receptor binding or binding proteins of skeletal growth factors present in the bone. Bone cells secrete a variety of growth factors and cytokines, but corticosteroids impact primarily insulin-like growth factors (IGFs) and transforming growth factor (TGF)-β. IGFs increase the synthesis of type I collagen by the osteoblast and bone matrix apposition rates, and decrease osteoblastic collagenase 3 expression and bone collagen degradation. Corticosteroids decrease IGF-I synthesis, which subsequently inhibits

osteoblastic cell replication and collagen synthesis, and increases collagenase-3 expression. Collagenase-3 is an enzyme that degrades type I and type II collagen and a loss of will result in less bone matrix for calcification[618].

In addition, corticosteroids can cause a loss of muscle mass and decreased muscle strength which may contribute to bone loss[614]. There is a striking association between the presence of steroid myopathy and osteoporosis[615].

In summary, the profound and rapid loss of bone induced by corticosteroids results from the convergence of systemic and direct skeletal effects, which lead to the development of osteoporosis. The most significant actions of corticosteroids are their inhibitory effects on bone forming cells, acting directly and indirectly by regulating the synthesis of factors present in the bone microenvironment. Defects in calcium transport lead to impaired gastrointestinal absorption of calcium, hypercalcuria, and secondary hyperparathyroidism. Parathyroid hormone increases the number of bone remodelling units. In the absence of sex hormones, bone is more susceptible to the effects of PTH. Bone resorption is enhanced and formation inhibited by corticosteroids at each remodelling site. Bone is being resorbed and the osteoblasts, inhibited by the direct effects of corticosteroids on recruitment and function, are incapable of replacing it. This combination of events results in rapid bone loss, which appears most marked during the first 6-12 months of corticosteroid therapy.

Clinical risk factors

Prospective studies in postmenopausal women have identified independent risk factors for fracture including age, sex, Caucasian race, history of prior fracture, recurrent falls, family history of fracture and poor health status. Although these risk factors have not

been evaluated in the context of corticosteroid-induced osteoporosis,[602] it is reasonable to consider them in the assessment of fracture risk in individuals treated with corticosteroids. Table 55 lists major risk factors for fracture. The major risk factors that are unique to corticosteroid-induced osteoporosis are dose, duration of therapy and route of administration.

Table 55 Major risk factors for fracture[630]

- Postmenopausal
- Increasing age
- Family history of osteoporosis
- High dose corticosteroids including inhaled steroids
- Low body weight (defined as body mass index <18)
- History of low trauma fracture
- Underlying disease associated with rapid bone loss (e.g. rheumatoid arthritis, immobilisation)
- Low calcium intake
- Male > 50 years
- Lifestyle factors including smoking, lack of exercise

Diagnostic threshold for BMD in corticosteroid users

The appropriate BMD threshold at which intervention should be considered in corticosteroid treated patients requires further evaluation and currently there are only expert opinions that dictate which patients should receive interventions based on their T-score. Based on the evidence that fractures occur at a higher BMD in corticosteroid-induced osteoporosis than in postmenopausal osteoporosis, a United Kingdom consensus group recommend the use of a T-score cut off of –1.5 SD below normal at the spine or hip as an indication for intervention in subjects taking corticosteroids.[622], whereas the

American College of Rheumatology proposed a T-score cut-off of –1 SD below normal[631]. The guidelines constructed by Osteoporosis Australia[630] recommended that patients with a T-score below –1.5 should be considered for prevention of bone loss and those with a score less than –2.5 should receive treatment. Whichever T-score is selected, its significance in terms of absolute fracture risk will differ according to age and hence the use of the T-score as an intervention threshold is not optimal[199]. For example, a T-score of –2 is associated with a 9% probability of an osteoporotic fracture in the next 10 years in non- corticosteroid treated women aged 50 years, but at the age of 80 years this probability is more than doubled (20.5%)[276].

It is recognised that there are limitations with the use of T-score interventional thresholds and the importance of other factors in the assessment of fracture risk. In the future it is likely that treatment thresholds will be based on fracture probability at different ages derived either from the T-score, the estimated relative risk or both[602].

Prevention and treatment

In the context of corticosteroid-induced effects on bone, the term prevention is generally used to denote of bone loss in individuals commencing corticosteroid therapy (primary prevention) whilst treatment describes the prevention of further bone loss and fractures in individuals already established on corticosteroid therapy, in whom low bone density and or fractures have developed (secondary prevention or treatment). Although this distinction does not currently have specific implications for the choice of intervention, it is important in making decisions about whether therapy should be instituted. At present three agents are licensed in Australia for corticosteroid-induced osteoporosis, namely alendronate, risedronate and cyclical etidronate[363].

Lifestyle measures

Although there are very few data on the effects of lifestyle interventions or modifications in corticosteroid-induced osteoporosis, it seems reasonable to recommend certain measures that may reduce bone loss and fracture risk. These include reducing the dose of corticosteroid to a minimum effective dose, the use of alternative routes of administration (e.g., inhaled or topical) or formulations (e.g., budesonide), and prescription of alternative immunosuppressive agents. Adequate amounts of dietary calcium intake should be encouraged and good nutrition and normal body weight (BMI 20-25 kg/m^2) should be maintained where possible. In addition, individuals taking corticosteroids should be advised to cease smoking and avoid excessive alcohol intake. Physical exercise should be encouraged if possible and a falls assessment risk should be performed in those at increased risk of falling (e.g., elderly).

Calcium

Attempts to prevent or reverse secondary hyperparathyroidism by improving calcium intake and reducing renal loss have been the mainstays of management of patients taking long-term corticosteroids. However, calcium when used alone in patients treated with long-term corticosteroids does not prevent bone loss and, at most, should only be considered adjunctive therapy in the treatment or prevention of corticosteroid-induced bone loss and should be administered in combination with other treatments[594, 632, 633].

Vitamin D ± Calcium

Buckley *et al*[634] reported in 1996 the results of a two-year randomised controlled trial demonstrating that calcium and vitamin D supplementation prevented bone in the lumbar spine and trochanter in rheumatoid arthritis patients receiving low dose corticosteroid treatment (mean dose 5.6 mg/day). Patients who received placebo lost bone at a rate of 2% and 0.9% per year in the lumbar spine and greater trochanter, respectively.

Other data support the effectiveness of calcium and vitamin D supplementation in preserving bone mass in patients prescribed long-term corticosteroid therapy. In a randomised placebo-controlled clinical trial of alendronate in the treatment of patients receiving corticosteroids (median prednisolone dose 11 mg/d), bone mass at the lumbar spine was maintained in the placebo group who received supplemental calcium and vitamin D[635]. Similarly, another trial found that the placebo treated patients (placebo and treatment groups also given supplemental calcium 1000 mg and 400 IU vitamin D) who were taking prednisolone (median dose 15 mg/day) had stable BMD at both the trochanter and lumbar spine.[595] Randomised controlled studies of active vitamin D alfacalcidiol at a dosage of 1 mcg/day and calcitriol at 0.5-1 mcg/day in addition to calcium have demonstrated prevention of bone loss, compared to calcium and placebo, in patients commencing corticosteroid therapy[632, 636].

Calcium and vitamin D therapy appears to be less effective than other agents in the prevention of corticosteroid-induce bone loss[637]. The Cochrane database reviewed five trials, which included 274 patients. The analysis was

performed at two years after starting calcium and vitamin D. This meta-analysis demonstrated a clinically and statistically significant prevention of bone loss at the lumbar spine and forearm with vitamin D and calcium in corticosteroid-treated patients. The authors concluded that because of low toxicity and cost, all patients being started on corticosteroids should receive prophylactic therapy with calcium and vitamin D. However, as Adachi stated[637], "the data are too limited to generally recommend them alone as a preventative therapy. Activated vitamin D may be of greater benefit". Having said that, Sambrook *et al*[638] recently completed a trial and found that there was no difference between simple vitamin D and calcitriol but that alendronate was superior to either treatment for corticosteroid -induced bone loss.

Bisphosphonates

Results from 5 large randomised controlled trials provide evidence that the bisphosphonates etidronate, alendronate, and risedronate are effective in both the prevention and treatment of corticosteroid-induced osteoporosis [594, 595, 635, 639, 640]. The bisphosphonates have the best quality of evidence for prevention of fractures secondary to corticosteroids (Table 56).

Table 56 Quality of evidence for the efficacy of pharmacological interventions in corticosteroid-induced osteoporosis[641]

Intervention	Spine BMD	Hip BMD	Vertebral Fracture	Nonvertebral Fracture
Calcium	-	-	-	-
Calcium + vitamin D	C	C	-	-
Hormone replacement therapy	B	D	-	-
Testosterone	B	-	-	-
Etidronate	A	A	B	-
Alendronate	A	A	B	-
Risedronate	A	A	A	-
Calcitriol	C	-	-	-
Alfacalcidol	A	C	-	-
Fluoride	B	-	-	-
Calcitonin	B	-	-	-

A, positive evidence from one or more, adequately powered, randomised, controlled trials; B, positive evidence from smaller nondefinitive randomised, controlled trials; C, inconsistent results from randomised controlled trials; D, positive results from observational studies

Alendronate

The principal evidence of effectiveness of alendronate, 5 or 10 mg/day, comes from a randomised placebo-controlled trial in which males and females (n = 477), either newly exposed to corticosteroids (34%) or established on therapy for greater than 4 months (66%), were studied, initially for 48 weeks. The mean BMD of the lumbar spine increased by 2% and 3%, respectively, in the groups that received 5 and 10 mg/day of alendronate, whereas the placebo group decreased by 0.4%. Each group received supplemental calcium (1000 mg) and vitamin D (250-500 IU). A similar pattern was seen at the femoral neck with a 1% increase in the treatment groups and a 1% decrease in the placebo group, with the treatment benefit being statistically significant.[635]

Although there were proportionally fewer new vertebral fractures in the alendronate group (2.3%) than the placebo group (3.7%), this difference did not reach statistical significance.

A subsequent 12-month extension trial in 208 patients continuing to receive at least 7.5 mg of prednisone or equivalent daily showed continued effectiveness in the second year. Over two years, lumbar spine BMD increased 2.8%, 3.9% and 3.7% in groups treated with daily doses of 5 mg or 10 mg for 2 years or 2.5 mg in year 1 and 10 mg in year 2, resulting in a statistically significant benefit of treatment when compared to the placebo group, in whom there was a non-significant reduction of 0.8%.[642] In patients receiving any dose of alendronate, BMD was increased at the trochanter ($p \leq 0.05$) and maintained at the femoral neck. Total body BMD was increased in patients receiving 5 or 10 mg alendronate ($p \leq 0.01$). There were fewer patients with new vertebral fractures in the alendronate group versus the placebo group (0.7% versus 6.8%; $p = 0.03$).

A significant benefit with one year's treatment of alendronate, 5 mg daily, on distal radius BMD was reported by Gonnelli *et al*[643] in patients commencing corticosteroid therapy for sarcoidosis. Also in a short study (6 months) investigating the effects of alendronate, 10 mg daily in patients with rheumatoid arthritis who were established on corticosteroid therapy, there was a significant increase in spine BMD from baseline but no significant benefit was demonstrated over the placebo group[644].

Sambrook *et al*[638] recently conducted a randomised, multicentre, open-label trial to compare the efficacy of alendronate, calcitriol, and simple vitamin D in the prevention and treatment of corticosteroid -induced bone loss. A total of 195 subjects (134 females and 61 males) commencing or already taking corticosteroids were randomised to one of three groups: calcitriol, 0.5 to 0.75 mcg/day; simple vitamin D (ergocalciferol, 30,000

IU weekly) plus calcium carbonate (600 mg daily); or alendronate, 10 mg/day plus calcium carbonate (600 mg daily). Over 2 years, the mean lumbar BMD change was +5.9% with alendronate, -0.5% with ergocalciferol, and -0.7% with calcitriol ($p < 0.001$). At the femoral neck, there was no significant difference in BMD change between the treatments over 2 years: alendronate (+0.9%), ergocalciferol (-3.2%), and calcitriol (-2.2%). Lumbar spine bone loss varied according to whether patients were starting or receiving chronic corticosteroids. Six of 66 calcitriol subjects, 1 of 61 ergocalciferol subjects, and 0 of 64 alendronate subjects sustained new vertebral fractures. These data do not suggest any difference between simple vitamin D and calcitriol but do show that alendronate was superior to either treatment for corticosteroid-induced bone loss.

Risedronate

In a trial in which patients receiving long-term corticosteroids for rheumatoid arthritis were randomised to treatment with 2.5 mg risedronate daily, 15 mg cyclical risedronate (daily for two weeks every 12 weeks) or placebo for approximately two years, BMD was maintained at the lumbar spine (mean +1.4%) and trochanter (mean +0.4%) in the 2.5 mg daily risedronate group, while significant bone loss occurred in the placebo group (mean -1.6% and –4.0% respectively)[645]. At the femoral neck, there was a non-significant bone loss in the 2.5 mg daily risedronate group (mean -1.0%) while in the placebo group bone mass decreased significantly (mean –3.6%). No significant treatment benefit was demonstrated in the group treated with cyclical risedronate.

Two separate randomised controlled trials have been reported involving a total of 795 premenopausal and postmenopausal women, in which 2.5 mg and 5 mg of risedronate daily were compared with placebo over a 12-month period. In a primary prevention study, in which all groups also received at least 500 mg calcium and 400 IU

of vitamin D, lumbar spine BMD fell significantly (mean -2.8%) in the placebo group, but the loss was prevented by both doses of risedronate. Significant differences were seen between risedronate 5 mg daily, and placebo at the lumbar spine (mean +3.8%), femoral neck (mean +4.1%) and femoral trochanter (mean +4.6%)[594].

Similar benefits were seen in a secondary prevention trial in patients with a variety of medical conditions who had been taking corticosteroids for six months or more at baseline. Bone mineral density increased significantly at the lumbar spine (mean +2.9%), femoral neck (mean +1.8%) and femoral trochanter (mean +2.4%) in the 5 mg risedronate group, these changes being significant when compared to the placebo group, in whom BMD did not change significantly in the spine or proximal femur[595]. Although not powered to show fracture efficacy, there was an observed reduction in the incidence of vertebral fractures of 70% in the combined risedronate treatment groups, relative to placebo ($p = 0.04$). In a post hoc analysis in which both these studies were combined there was a significant reduction in vertebral fracture rates in the 5 mg treatment group (5.4%) compared to the placebo group (16.2%)[646].

Etidronate

Cyclical etidronate was initially shown to be effective in a small single-blinded primary prevention study in 20 elderly women with giant cell arteritis. A significant increase in lumbar spine BMD (mean +1.4%) was seen over 12 months in the intervention group whereas the placebo group observed a mean 5% reduction in spine BMD[647]. Subsequent results from a larger primary prevention study have been reported.

In a 12-month randomised placebo-controlled study involving 141 men and women recently commencing corticosteroids, small and insignificant mean increases in BMD of 0.6% at the lumbar spine and 1.5% at the trochanter occurred in patients with a

variety of medical conditions. The placebo group, however, lost bone at both sites with significant differences between active and placebo groups of 3.7% (p = 0.02) and 4.1% (p = 0.02) at the lumbar spine and trochanter respectively[639]. A significant reduction in vertebral deformity and subjects with new vertebral fracture in the treatment group after one year was demonstrated in a post-hoc analysis, although the validity of these data has been questioned because of differences in the baseline characteristics of the treatment and control groups[633, 648]. A subsequent 12-month randomised controlled trial in 117 patients starting high-dose corticosteroids for a variety of medical conditions showed similar effects of cyclical etidronate at the lumbar spine but failed to show any significant difference in BMD between treatment and control groups at the femoral neck or trochanter[640].

Other bisphosphonates

Other bisphosphonates used in the treatment and prevention of corticosteroid-induced osteoporosis include pamidronate[649-652], clodronate[653, 654], and ibandronate[655]. There have been no studies conducted using zolendronate in the treatment or prevention of corticosteroid-induced osteoporosis.

Hormone replacement therapy

All patients receiving long-term corticosteroid therapy should be assessed for hypogonadism, and when present, this should be corrected if possible.

There have been a few studies on the use of HRT in corticosteroid -induced osteoporosis. Currently, there are no published reports regarding efficacy of HRT in preventing bone loss at the initiation of corticosteroid therapy. Hall *et al*[656] performed a

randomised trial of transdermal oestradiol 50 mcg/day, with oral norethisterone 1 mg daily for 12 days per cycle versus calcium in a group of postmenopausal women with rheumatoid arthritis, 21% whom were treated with corticosteroids. In the subgroup of patients taking corticosteroid therapy, there were mean increases in lumbar spine BMD and femoral neck BMD (3.8% and 1.6% respectively) compared to the calcium treated patients who experienced changes of –0.85% and +1.1%, respectively. These changes were statistically different at 24 months. In another randomised study, Coombes *et al*[657] investigated the effects of tibolone 2.5 mg/day in a small (n=37) sample of postmenopausal women with rheumatoid arthritis, all who were receiving long-term corticosteroid therapy. After 24 months treatment significant treatment benefits were observed in the spine (mean BMD increase 4% versus placebo) and at the hip (mean increase 4.2% versus placebo)

In a study conducted by Kung *et al*[658], 28 young hypogonadal women with systemic lupus erythematous treated with long-term corticosteroid therapy were randomised to receive HRT (conjugated oestrogen 0.625 mg/day for 21 days per cycle and medroxyprogesterone 5 mg/day on days 10-21 of cycle) or calcitriol 0.5 mcg/day. After two years therapy, lumbar spine BMD had increased by a mean of 2% in the HRT group and decreased by 1.7% in the calcitriol group ($p = 0.03$). There was no significant change in the femoral neck for either group.

The effects of testosterone were investigated by Reid *et al*[659] in a small sample of 15 asthmatic men who had received long-term corticosteroid therapy. A significant benefit was seen in the men who received testosterone (testosterone esters 250 mg/month as intramuscular depot injection) for 12 months in lumbar spine BMD with a mean increase of 5% versus no change in controls ($p<0.05$). There was no significant benefit demonstrated at the femoral neck.

Calcitonin

A recent meta-analysis of 9 studies demonstrated that calcitonin appears to preserve bone mass in the first year of glucocorticoid therapy at the lumbar spine by about 3% compared to placebo, but not at the femoral neck. The analysis suggested that the protective effect on bone mass may be greater for patients who have been taking corticosteroids for more than three months. Efficacy of calcitonin for fracture prevention in steroid-induced osteoporosis remains to be established[660].

Studies of the effect of intranasal or subcutaneous calcitonin on corticosteroid - induced bone loss have produced conflicting results. A significant treatment benefit has been demonstrated in lumbar spine BMD but not femoral neck when compared to controls in patients who have had prolonged corticosteroid therapy[661-664]. However, no effect on spine BMD was demonstrated in other studies[652, 665, 666]. Other studies performed in patients undergoing organ transplantation failed to show a significant effect of treatment on BMD[667-671].

Parathyroid hormone

There are little data on the use of PTH peptide 1-34 in patients prescribed long-term corticosteroids. Lane *et al*[672, 673] reported the effects of PTH-peptide 1-34 in 51 postmenopausal women with chronic inflammatory diseases treated with oestrogen and corticosteroids. Significant increases in spinal BMD were seen at 12 months with a mean increase of 11% compared to the control group, while there was no significant benefit in BMD at the hip. During the 12 months when PTH-peptide 1-34 treatment was ceased, spine BMD remained stable, thus maintaining the treatment benefit.

Interestingly, hip BMD increased so that at 24 months total hip BMD was significantly greater (+5%) in the PTH group than those receiving HRT alone[674].

Fluoride

Fluoride is a potent anabolic factor for bone cells. Its bone-forming effect is mediated through an increased osteoblastic cell proliferation[675]. Fluoride, a potent anabolic agent, has been evaluated in a number of randomised trials in patients using corticosteroids for various indications[676-682]. In most of these studies, fluoride was given alone (with or without calcium ± vitamin D) but in two studies it was used in combination either with cyclic etidronate[681] or calcifediol[679]. In all studies in which spine BMD was assessed, significant treatment benefits of fluoride were demonstrated after one or two years treatment with one study demonstrating a mean increase of 11%[682]. No significant benefit has been shown in those studies that measured hip BMD[676-682]. Furthermore, there are not adequate data from these small randomised clinical trials in patients receiving corticosteroids to warrant conclusions about the ability for fluoride to reduce vertebral fractures[675]. In addition, fluoride therapy is associated with significant side effects. The most frequent is upper abdominal discomfort due to chemical gastritis resulting from the effect of hydrofluoric acid on the gastric mucosa. The other major side effect is the so-called 'painful lower extremity syndrome', that is characterised by acute pain, tenderness and swelling in the lower extremities. It often requires withdrawal from therapy[675]. For these reasons fluoride is *not* routinely used for osteoporosis therapy.

Raloxifene

There have been no trials investigating the use of raloxifene in corticosteroid-treated patients. However a trial in postmenopausal women treated with corticosteroids suggested that that raloxifene may prevent spinal bone loss[683].

Other agents

Vitamin K use has been reported in patients taking corticosteroids but there is insufficient data to enable evaluation due to the short (10 weeks) duration of the study, although indications suggested that there is benefit of using vitamin K to prevent spinal bone loss[684].

Future therapies

There is considerable interest in the use of corticosteroids with potent anti-inflammatory and immunosuppressive actions but with fewer adverse skeletal effects than prednisolone. These include deflazacort and budesonide[602].

Guidelines for prevention and treatment

The American College of Rheumatology

In 1996, the American College of Rheumatology (ACR) summarised available information about the pathophysiology, diagnosis, prevention, and treatment of corticosteroid-induced osteoporosis and developed recommendations for clinical practice[685]. In 2001 the ACR Ad Hoc Committee on corticosteroid-induced osteoporosis, updated and reviewed these guidelines[631]. These are shown in Table 57.

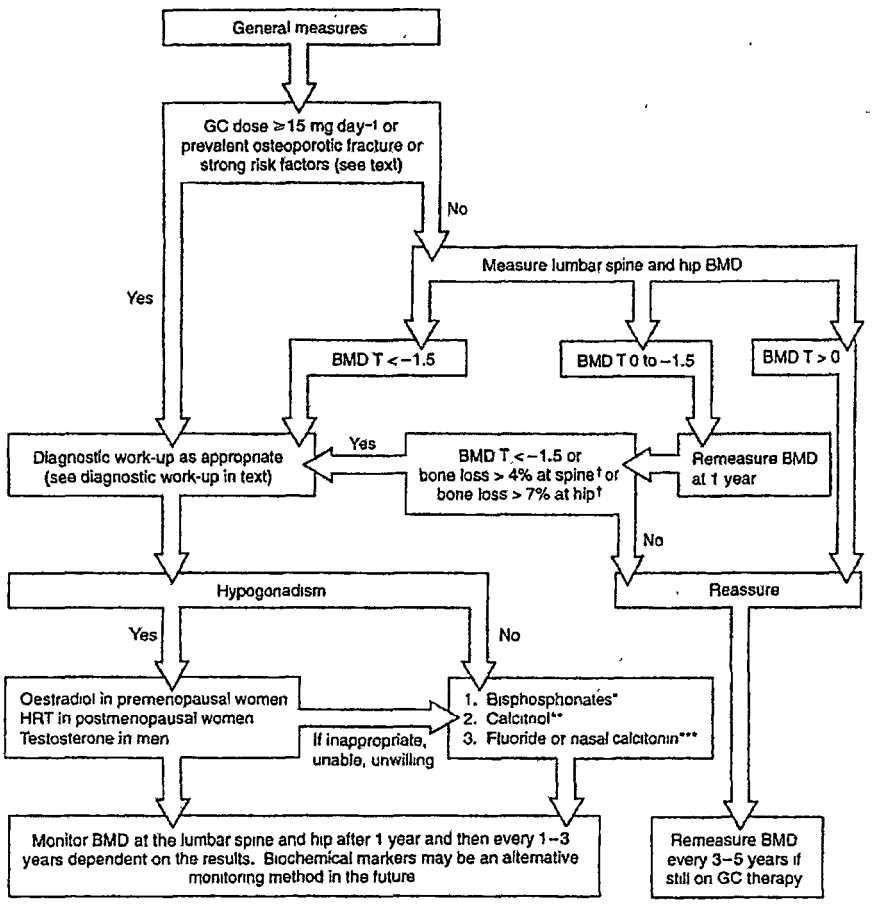
Table 57 American College of Rheumatology's recommendations for the prevention and treatment of corticosteroid-induced osteoporosis[631]

Patient begining therapy with glucocorticoid (prednisone equivalent of ≥5 mg/day) with plans for treatment duration of ≥3 months:
Modify lifestyle risk factors for osteoporosis.
Smoking cessation or avoidance
Reduction of alcohol consumption if excessive
Instruct in weight-bearing physical exercise.
Initiate calcium supplementation.
Initiate supplementation with vitamin D (plain or activated form).
Prescribe bisphosphonate (use with caution in premenopausal women).
Patient receiving long-term glucocorticoid therapy (prednisone equivalent of ≥5 mg/day):
Modify lifestyle risk factors for osteoporosis.
Smoking cessation or avoidance
Reduction of alcohol consumption if excessive
Instruct in weight-bearing physical exercise.
Initiate calcium supplementation.
Initiate supplementation with vitamin D (plain or activated form).
Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated.
Measure bone mineral density (BMD) at lumbar spine and/or hip.
If BMD is not normal (i.e., T-score below −1), then
Prescribe bisphosphonate (use with caution in premenopausal women).
Consider calcitonin as second-line agent if patient has contraindication to or does not tolerate bisphosphonate therapy.
If BMD is normal, follow up and repeat BMD measurement either annually or biannually.

The National Osteoporosis Society (UK) Guidelines

The National Osteoporosis Society in the United Kingdom has published guidelines (Figure 41) on the prevention and management of corticosteroid-induced osteoporosis[622]. The algorithm is for the prevention and treatment of osteoporosis in patients receiving an oral corticosteroid equivalent to 7.5 mg of prednisolone per day for six months or more.

Figure 41 National Osteoporosis Society (UK) guidelines for the management of corticosteroid-induced osteoporosis[622]

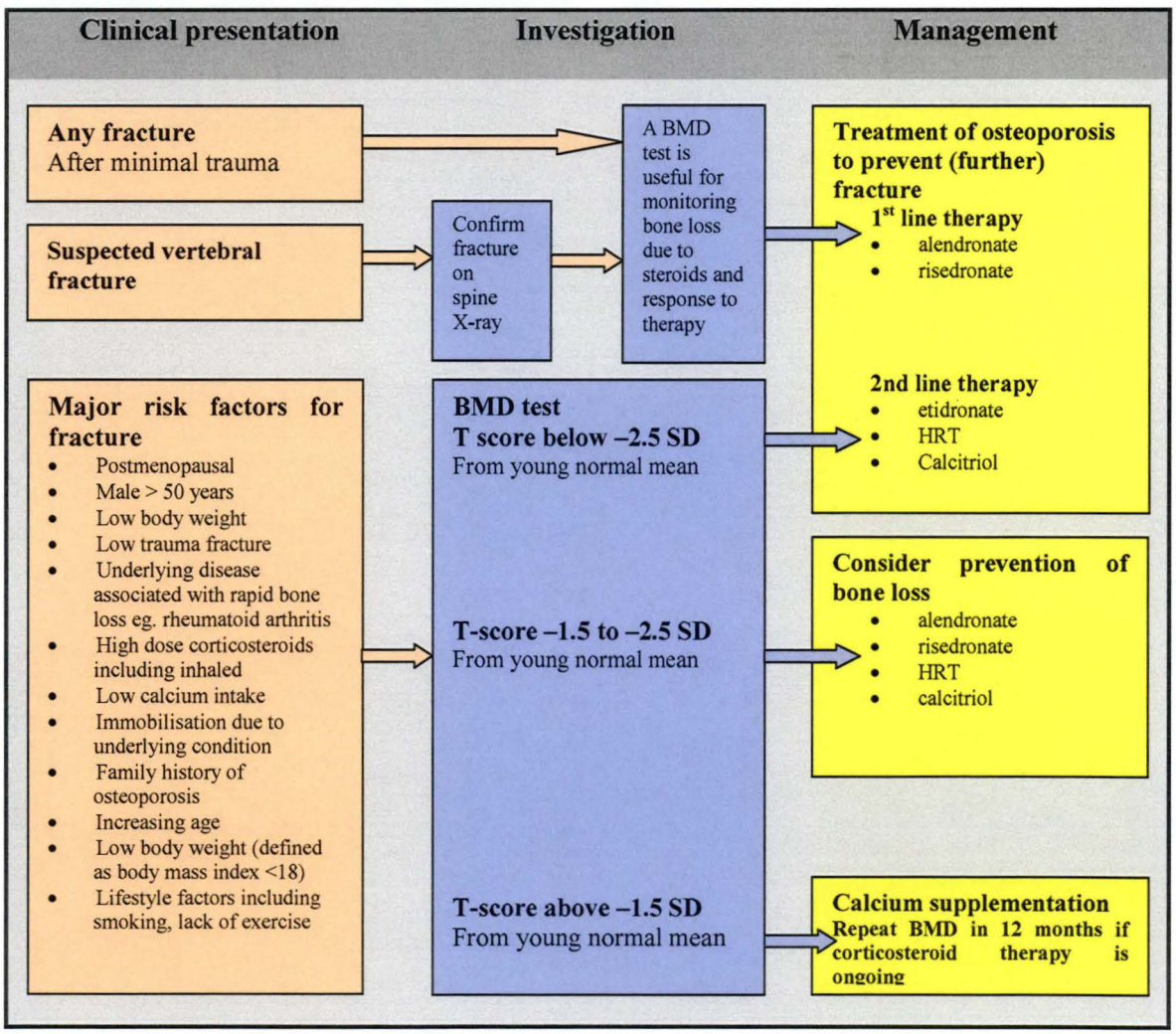


* Use in caution in women of child-bearing age.
** Monitor serum calcium at 4 weeks, 3 & 6 months and at 6 monthly intervals thereafter Not currently licensed for the prevention or treatment of GC osteoporosis.
*** Not currently available or licensed for use in the UK. However, represent alternative therapeutic options.
† These changes are in excess of the least significant change.

Osteoporosis Australia

In August 2001, Osteoporosis Australia published guidelines on the management and prevention of corticosteroid-induced osteoporosis (Figure 42)[630]. The guidelines recommend patients who are treated with 7.5 mg or more of oral prednisolone (or equivalent) or 800 mcg or more of budesonide or beclomethasone (or equivalent) a day should undergo bone densitometry.

Figure 42 Australian corticosteroid-induced osteoporosis guidelines for management[630]



Underrecognition of corticosteroid-induced osteoporosis

A recent study by Hougardy *et al*[52] revealed clear evidence of underutilisation of osteoporosis agents in patients presenting to a major academic hospital in Hobart, Tasmania, Australia. The median age of the patients was 69 years (range: 15-90 years) and 58% were female. Over half (53%) of the patients were on oral corticosteroids only, with 26% using inhaled corticosteroids only, and 21% on both oral and inhaled corticosteroid therapy. The most common conditions for which patients were receiving corticosteroid therapy were asthma (37% of patients), chronic obstructive pulmonary disease (33%) and rheumatoid arthritis (17%). The most commonly used oral corticosteroid was prednisolone (93%), the median daily dose was 10 mg prednisolone equivalent, and the median duration of oral corticosteroid treatment was 50 weeks. Almost one-third (31%) of the patients receiving oral corticosteroid treatment had been taking the equivalent of 7.5 mg prednisolone daily for at least 6 months. Only 11% of all patients on oral corticosteroids and 21% of those who had been taking oral corticosteroids for at least one year had documented evidence of BMD testing being performed in the past in the hospital. Only 21% of all patients on oral corticosteroids and 31% of those who had been taking oral corticosteroids for at least one year were receiving medication for osteoporosis prevention.

There have been many studies that have identified that users of long-term oral corticosteroids do not receive adequate preventive therapy against osteoporosis.[574, 686-692]

Buckley *et al*[687] concluded that many patients receive inadequate treatment to prevent corticosteroid-induced osteoporosis, and a broad educational effort is needed to ensure that osteoporosis prevention becomes the standard of care for patients receiving long-term corticosteroid treatment. Likewise, Hart *et al*[691] found underuse of

osteoporosis prevention and suggested that osteoporosis prophylaxis during steroid treatment be promoted by local hospital guidelines, hospital and community pharmacists, audit, and GPs. A suitable way to educate patients about corticosteroid-induced osteoporosis might be through pharmacies as described by Lips[693] who suggested that "every first prescription of corticosteroid could be accompanied by a leaflet on the risks of osteoporosis and appropriate guidelines". Perhaps the most attention ought to be directed at changing the behaviour of doctors who prescribe corticosteroids.

Influencing prescribing behaviour

Background

There is a plethora of evidence that conditions, as discussed previously in this thesis, are often not diagnosed or are undertreated. For example, many patients are not optimally treated for hypertension[13-15], hyperlipidaemia;[16-18], heart failure;[19-21] and osteoporosis[38-52]. This is often despite clear guidelines or evidence that practice ought to change.

There is increasing recognition of the failure to translate research findings into practice[694]. Consequently, efforts have been made to alter prescribing behaviour to translate research findings into practice. Although many guidelines are available, some are better adhered to in practice than others[695]. This difference could be caused by various reasons, such as type of health problem addressed, method of development used, content of the recommendations, the method of dissemination, or the format and layout[696].

A systematic review of promising approaches to influencing prescribing behaviour suggested the use a variety of interventions including audit and feedback, reminders, and educational outreach also known as "academic detailing"[697].

"Academic detailing" is a process by which a healthcare provider is visited by a trained person in his or her own setting, and has been identified as an intervention that may improve the practice of health care professionals, in particular prescribing. Academic detailing was first coined in the 1980's by Soumerai and Avorn[698], and it was suggested by Soumerai *et al*[699] in the late 1980's that academic detailing had the potential to change health professional practice, especially in relation to prescribing practices of physicians[700].

Barriers to implementation of evidence

Analysis of barriers to changing practice has shown that obstacles to change practice can arise at different stages in the health-care system, at the level of the patient, the individual professional, the health-care team, the health-care organisation, or the wider environment (Table 58)[701]. Most theories on implementation of evidence in health care emphasise the importance of developing a good understanding of such obstacles to develop an effective intervention[701]. Others have stated that as long as continuous professional development remains a private issue for doctors, and there are no financial mechanisms to compensate for time invested and income lost, any educational intervention will have a limited effect[702].

Table 58 Example of barriers to implementation of evidence[701]

Practice environment (organisational context)
• Financial disincentives – eg, lack of reimbursement
• Organisational constraints – eg, lack of time
• Perception of liability – eg, risk of formal complaint
• Patient expectations – eg, expressed wishes related to prescription
Prevailing opinion (social context)
• Standards of practice – eg, usual routines
• Opinion leaders – eg, key persons not agreeing with evidence
• Medical training – eg, obsolete knowledge
• Advocacy – eg, by pharmaceutical companies
Knowledge and attitudes (professional context)
• Clinical uncertainty – eg, unnecessary test for vague symptoms
• Sense of competence – eg, self confidence in skills
• Compulsion to act – eg, need to do something
• Information overload – eg, inability to appraise evidence

Interventions used to improve physician prescribing

The number of original studies and systematic reviews about the effectiveness of different interventions to change clinical practice is growing, which assists in the selection of appropriate strategies. An overview of strategies for implementation of evidence and the conclusion of reviews is shown in Table 59. There is more evidence on professional-oriented interventions (education, reminders, feedback) than on those aimed at the organisation or the patient. Economic assessment of performance strategies is scarce, as is information on patients'outcomes[701]. Interventions targeted at specific obstacles to change seem to be more effective than interventions that are not[701].

Multifaceted interventions are more likely to be effective than single interventions[703-705] although they are likely to be more expensive[697].

Educational strategies

A comprehensive review[697] concluded that there was little evidence that the passive dissemination of consensus recommendations alone resulted in provider behaviour change. The authors stated that guidelines can change clinical practice but were more likely to be effective if they took into account local circumstances, delivered by educational interventions and were implemented by patient-specific reminders. There is inconclusive evidence whether guidelines developed by end users were more likely to be effective than those not developed by end users[697]. The authors concluded that there are no "magic bullets" for changing provider behaviour: a range of interventions could lead to change, but no single intervention was always effective for changing behaviour[697]. Mailed educational materials alone were generally ineffective, while educational outreach approaches and ongoing feedback were usually effective[697].

Thomson and associates[704] reviewed the effectiveness of educational outreach visits. Most observed statistical improvements in care (especially when social marketing techniques were applied), although the effects were small to moderate. Educational outreach by trained facilitators or experts was observed to be more effective than audit and feedback, although the cost effectiveness of educational outreach was unclear. Use of local opinion leaders has resulted in mixed effects. Thomson and associates found that local opinion leaders were more effective than audit and feedback in one study, although further research was required before widespread use of this intervention could be justified[706].

Large conferences and courses demonstrate mixed results; small group interactive education with active participation showed positive effects[701].

Audit and feedback

Sixteen reviews have judged audit and feedback with mixed results[701]. This intervention appears effective when targeting test ordering and prevention, but the effect size could be moderated by type of feedback, its source and format, and frequency or intensity of presentation. Feedback is recommended with education, outreach visits, or reminders[701]. A Cochrane review concluded that audit and feedback is more likely to be effective when the baseline adherence to recommended practice is low[707].

Use of reminders and computers

A general effect of reminders has been noted in a number of reviews. In one review, reminders were shown to have the greatest effect of all interventions studied[701]. A review by Balas[708] of 98 trials showed that three-quarters had a substantial improvement with computer decision support and reminders. Results of different systematic reviews

suggested that computerised decision support is more likely to be effective for management decisions than for diagnosis and that simple prompting systems show more positive results than knowledge-based and advanced systems[701]. Hunt[709], Walton[710] and colleagues showed that computerised decision support is most effective for drug dosing and preventive care. A recent randomised controlled study[702] conducted in Germany, found that a knowledge increase was not achieved through dissemination of computerised guidelines in general practice.

Other interventions

There have been reviews investigating the effect of the expanding role of other health professionals and their role on influencing patient outcomes. For example, the expanding role of a pharmacist has been shown to positively alter the prescribing behaviour of doctors[701]. The role of nurses in influencing physician behaviour has been mixed[701].

Table 59 Overview of interventions to promote professional behavioural change that could be used to implement research findings[701]

Strategy	Number of reviews*	Number of studies	Conclusions
Educational materials	9	3-37	Mixed effects
Conferences, course	4	3-17	Mixed effects
Interactive small group meetings	4	2-6	Mostly effective, but limited number of studies
Educational outreach visits	8	2-8	Especially effective for prescribing/prevention
Use of opinion leaders	3	3-6	Mixed effects
Education with different educational strategies	8	5-63	Mixed effects, dependent on combination of strategies
Feedback on performance	16	3-37	Mixed effects, most effect for test ordering
Reminders	14	4-68	Mostly effective, particularly for prevention
Computerised decision support	5	11-98	Mostly effective for drug dosing and prevention
Introduction of computers in practice	2	19-30	Mostly effective
Substitution of tasks	6	2-14	Pharmacist: effect on prescribing; nurse: mixed results
Multiprofessional collaboration	5	2-22	Effective for a range of different chronic conditions
Mass media campaigns	1	22	Mostly effective
Total quality management/continuous quality improvement	1	55	Limited effects, mostly single-site non-controlled studies
Financial interventions	6	3-89	Fundholding and budgets effective, mainly on prescribing
Patient-mediated interventions	8	2-14	Mixed effects; reminding by patients is effective in prevention
Combined interventions	16	2-39	Most reviews: more effective than single interventions; not confirmed in recent reviews

* Number of reviews that included studies addressing the interventions

Previous interventions to promote prevention of corticosteroid-induced osteoporosis

There has been no research published on the effect of any intervention to increase the prescribing of preventive agents for corticosteroid-induced osteoporosis.

Aim of study

The aim of this project was to assess the usefullness of a comprehensive educational programme in increasing the use of osteoporosis preventive therapy in patients prescribed long-term oral corticosteroids.

Chapter 2: Methods

Production of guidelines

A composite version of the guidelines produced by the American College of Rheumatology[631], a UK Consensus Group on the management of glucocorticoid-induced osteoporosis[622] and Osteoporosis Australia[630] was developed for local use in consultation with medical specialists (Figure 43). The intervention study was conducted in southern Tasmania (population 230,000), using the northern region of the State as the control area (population 130,000). The guidelines, with an explanatory covering letter (Appendix 19), were sent to each GP (approximately 270) practicing within southern Tasmania, using the Medical Council of Tasmania's 'Register of Legally Qualified Medical Practitioners', in October 2001. The results of a recent local study showing evidence of under utilisation of both monitoring of bone mineral density and prescribing of recommended osteoporosis-preventing agents[52], were emphasised.

Academic detailing visit

During January to May 2002 all GPs in southern Tasmania were contacted to arrange a time to discuss corticosteroid-induced osteoporosis. The research pharmacist (MN) then visited each GP and discussed the rationale of prescribing osteoporosis preventive therapies and treatment to patients receiving long-term oral corticosteroids. Additional reference material was provided whenever requested, for example, the Australian or American guidelines. Each GP was also given a wallet-sized card containing the guidelines with some brief points on the reverse side to highlight the importance of preventing osteoporosis (Figure 44).

Figure 43 Guidelines that were distributed to doctors and pharmacists

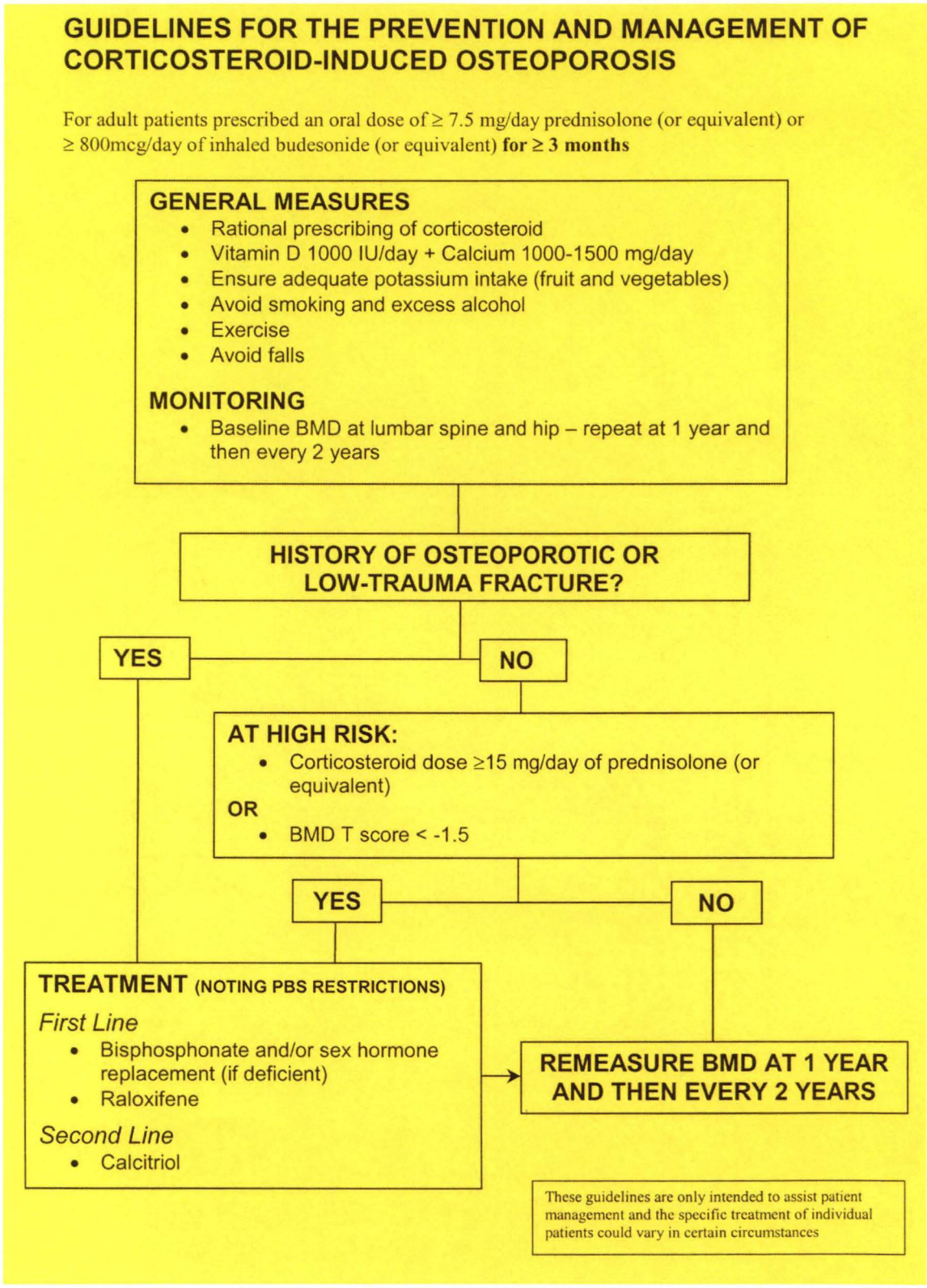
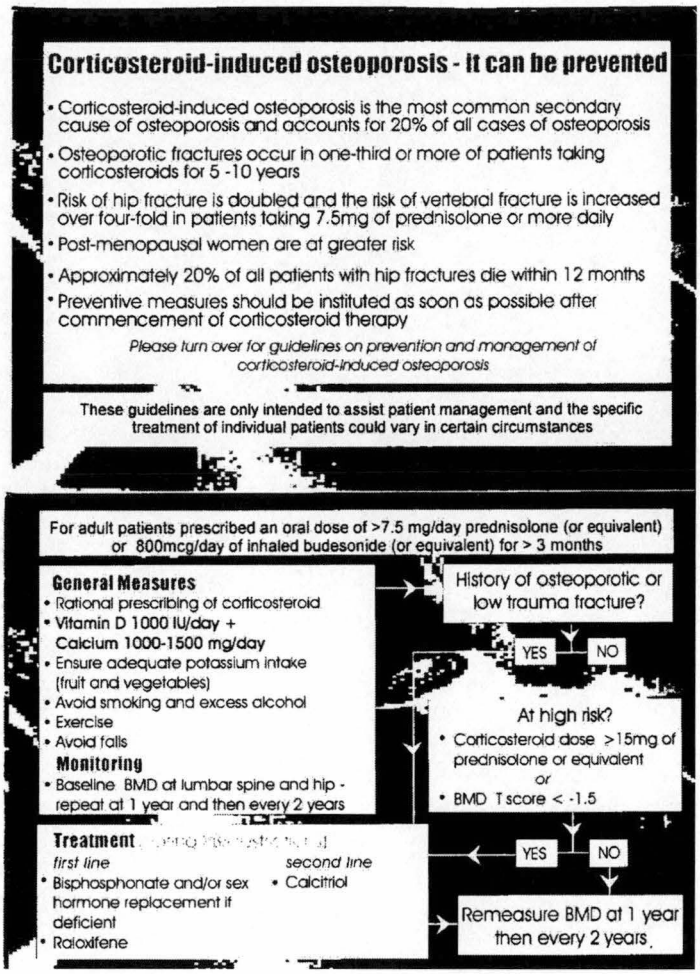


Figure 44 Guidelines embossed on a wallet-sized card that were provided to GPs



The guidelines were also sent to all community pharmacies in southern Tasmania (n = 69) with an explanatory covering letter (Appendix 20). All the pharmacies were subsequently visited and the pharmacist on duty was detailed on the guidelines. Each pharmacy was also given a supply of refrigerator magnets (Figure 45) intended for supply to patients presenting to the pharmacy with a prescription for an oral corticosteroid drug (and who had been taking it for longer than three months or who were undergoing treatment expected to last for longer than three months). Whilst the

academic detailer was in the pharmacy, shelf markers were also placed b elow the different brands of oral corticosteroids, to serve as a reminder for pharmacists when they selected the products from the shelf for dispensing (Figure 46). Pharmacists were also provided with further written material if requested, including a paper published in *Australian Pharmacist*[179], specifically addressing the importance pharmacists have in advising patients on osteoporosis prevention if treated with corticosteroids.

Figure 45 Refrigerator magnet supplied to community pharmacists for distribution to patients prescribed long-term corticosteroids

Figure 46 Shelf marker placed in community pharmacies where corticosteroids stored to remind pharmacists to discuss osteoporosis prevention with patients

IS PATIENT ON LONG-TERM CORTICOSTEROIDS? CONSIDER OSTEOPOROSIS PREVENTION !

Participating GPs and pharmacists were anonymously surveyed (using a visual analogue scale) to assess the usefulness of the mailed information and academic detailing visit (Appendix 21, Appendix 25). In particular, GPs were asked if they were more likely to consider preventive therapy in their patients on corticosteroids, following the educational programme. Pharmacists were asked if they were more likely to discuss preventive measures in patients taking oral corticosteroids and to refer patients to a GP when appropriate. The completed evaluation forms were returned via reply-paid envelopes.

Outcome measures

Two sources of prescribing data were utilised to measure the outcome of the educational intervention. As in a previous study,[52] data were collected on patients admitted to the Royal Hobart Hospital, a 400-bed acute care academic hospital and the only major public hospital in the southern region of Tasmania. The baseline sample consisted of all adult patients who had been taking oral corticosteroids for at least three months (as identified from medical records and drug charts) and who were admitted to the medical wards of the hospital during the period 1st April 2001 to 30th September 2001. The only exclusions were patients whose medical records were incomplete, those who were receiving oral corticosteroids for palliative care, or those who were unable to answer questions about their therapy.

Variables recorded for each patient included demographic information, reason for admission to hospital, smoking and alcohol intake, medical history, medication history on admission, bone densitometry data when available, and drug therapy on

discharge from hospital. Concurrent medications that either increased the risk of osteoporosis (e.g. loop diuretics, anticonvulsants) or increased the risk of falls (e.g. benzodiazepines, tricyclic antidepressants) were recorded. The patients were also asked a short series of questions during their hospitalisation to extract some of the relevant information (e.g. level of sun exposure per week, family history of osteoporosis, whether they had ever sustained a low trauma fracture). Approximately one month following the completion of the academic detailing phase of the project, follow-up data were again collected on consecutive adults admitted to the Royal Hobart Hospital who had been taking oral corticosteroids for at least three months. This procedure was identical to that for the baseline data collection.

The percentage of patients prescribed long-term corticosteroids and concurrently prescribed therapy to treat or prevent osteoporosis (calcium, vitamin D, bisphosphonates, raloxifene, HRT) were compared before and after the intervention.

Pharmaceutical Benefit Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) dispensing data were also obtained from the Department of Health & Ageing, for alendronate, risedronate, etidronate, raloxifene, calcitriol, calcium carbonate and prednisolone for the North of Tasmania (postcodes 7200-7299; control region) and South of Tasmania (7000-7199; intervention region) for March-August 2001 and March-August 2002. We did not include the use of hormone replacement therapy or testosterone therapy in dispensing data analysis because these medications are primarily used for indications other than osteoporosis prevention or treatment in Australia. Data were unavailable on the use of vitamin D, which is not listed on the PBS or RPBS.

The unit quantities of each drug dispensed were converted to defined daily doses (DDDs)[711]. The key outcome measure examined was the change in total DDDs of

osteoporosis preventive therapy, expressed as a ratio to the total DDDs of prednisolone between the north and south of Tasmania during the aforementioned study periods.

Statistical analysis

Non-parametric techniques were principally used to describe patient characteristics and examine differences in variables between sub-groups of patients. Statistical comparisons for drug dispensing data were made between the different areas of the State (i.e. south/intervention region versus north/control region), both before and after the intervention, and within each study area (before versus after the intervention) using a Normal approximation to the Binomial distribution. A p value less than 0.05 was considered statistically significant. The statistical analysis was performed using Statview® 5.01 (Abacus Concepts Inc., Berkeley, CA, United States).

Ethics approval

The study was approved by the Research and Ethics Committees of the Royal Hobart Hospital prior to its commencement. The Division of General Practice (Southern Tasmanian Division), the Pharmacy Guild of Australia, and Osteoporosis Australia also supported the project.

Chapter 3: Results

During the academic detailing period 200 GPs (74% of those in southern Tasmania) and 69 pharmacies (81 pharmacists) were visited and the guidelines discussed. Each GP visit was approximately 15 minutes in duration. There was an evaluation survey response of 83% for GPs and 47% for pharmacists. The sessions were favourably accepted by GPs, with a median score of 8 (range 1 - 10) on the visual analogue scale (0 = not useful, 10 = very useful) when asked whether the detailing had been useful. Pharmacists also found the session useful, with a median score of 8 on the scale (range 5.5 - 10).

The GPs and pharmacists were also asked to indicate whether they had routinely considered osteoporosis prevention in patients prescribed long-term corticosteroids (where 0 = strongly disagree and 10 = strongly agree). The GPs' median score was 6.5 (range 0.5 - 10) and the pharmacists' median score was 2.5 (0 - 8). Both the GPs and pharmacists were asked whether they agreed or disagreed that they were more likely to consider preventive therapy in patients prescribed long-term corticosteroids after being exposed to the educational programme. The median score (0 = strongly disagree, 10 = strongly agree) for GPs and pharmacists was 8.5 (range 0 - 10) and 9 (6 - 10), respectively.

In the hospital-based study, a total of 233 patients were included - 113 and 120 patients in the pre-intervention and post-intervention groups, respectively. The two groups were very similar with regard to key sociodemographic and clinical variables (Table 60). Patients in the post-intervention group were significantly more likely to have been prescribed some form of antiresorptive therapy than the pre-intervention group on presentation to hospital (57% v 31%, $p < 0.0001$). In particular, patients were more likely to be prescribed a bisphosphonate following the intervention (6% in the pre-

intervention v 24% in the post-intervention group; $p < 0.001$; Table 61). There were smaller, but statistically significant, increases in the use of calcium (5% v 19%; $p < 0.01$), vitamin D (3% v 11%; $p < 0.05$) and hormone replacement therapy (5% v 14%; $p < 0.05$) after the intervention. There was no change in the use of calcitriol following the intervention (17% v 15%; $p = 0.7$).

Approximately 29% of patients who were prescribed at least 7.5 mg of prednisolone (or equivalent) daily were receiving osteoporosis preventive therapy in the baseline group, and this significantly increased to 51% of the post-intervention group ($p < 0.01$). Approximately 34% of patients who had been on oral corticosteroids continuously for at least 12 months in the pre-intervention group were receiving preventive medication, compared to 61% in the post-intervention group ($p < 0.001$). The use of preventive therapy was more common in females in both groups of patients. In the baseline group, 39% of females were receiving preventive therapy compared with 18% of males ($p < 0.05$), while the matching figures in the post-intervention group were 64% and 44% ($p < 0.05$).

PBS and RPBS data were obtained from the Commonwealth (Table 62). The prescribing of osteoporosis preventive agents relative to prednisolone was very similar in the two regions during the baseline period ($z = 0.34$, $p = 0.7$). At follow-up, however, the prescribing of osteoporosis preventive agents relative to prednisolone was significantly higher in the intervention region ($z = 2.17$, $p < 0.05$). The prescribing of osteoporosis preventive agents relative to prednisolone increased in both regions over the course of the study, but particularly in the intervention region (control: $z = 1.87$, $p = 0.06$ and intervention: 4.42, $p < 0.0001$). The largest relative increases occurred with calcium (increased by 22% in the intervention region, with no change in the control region) and raloxifene (increased by 38% in the intervention region and 6% in the

control region). The use of bisphosphonates (alendronate, risedronate, and etidronate) increased markedly in both regions (increase by 119% in the intervention and 123% in the control region).

Table 60 Hospital patient characteristics before and after the intervention

	Baseline (n = 113)		Post-intervention (n = 120)	
Female (%)	61		62.5	
Age; years (median & range)	71	(20 - 93)	70	(20 - 92)
Aged > 65 years (%)	63		63	
Smoker (%)	23		19	
Ex-smoker (%)	52		54	
Median corticosteroid daily dose on admission (mg; range)[a]	10	(2 - 50)	7.5	(3 - 100)
Usual median daily dose (mg; range)[a]	7.5	(2 - 50)	7.5	(3 - 100)
Usual median dose > 7.5 mg daily (%)[a]	56		52	
Median time of continuous oral corticosteroid use (months; range)	60	(3 - 480)	60	(3 - 372)
Median number of chronic medical conditions (range)	4	(1 - 10)	4	(1 - 12)
Median number of medications on admission	8	(2 - 19)	8.5	(1 - 26)
Documented osteoporosis (%)	24		33	
Hypogonadism (%)				
males	7		9	
females (menopause < 45 years)	38		31	
Indication for corticosteroid use (%)[b]				
asthma	11		8	
chronic obstructive pulmonary disease	27		21	
rheumatoid arthritis	27		27	
inflammatory bowel disease	4		5	
muscular/connective tissue disease	23		23	
temporal arteritis	5		4	
other	17		20	
Previous fracture (%)	41		43	
If yes - while on corticosteroids (%)	80		83	
Low sun-exposure[c]	38		43	
Family history of osteoporosis	10		13	
Taking other medications that increase the risk of osteoporosis (%)	41		47	
Taking medications that increase the risk of falls (%)	83		79	
Receiving osteoporosis preventive therapy (%)	31		57	

[a] Prednisolone or equivalent.
[b] Some patients had more than one indication.
[c] Patients who were not exposed to at least one hour of sunlight a week[340].

Table 61 Use of osteoporosis preventive therapy in hospital patients before and after the intervention

Preventive Therapy[a]	Baseline (%)		Post-intervention (%)	
	Admission (n = 113)	**Discharge (n = 108)**	**Admission (n = 120)**	**Discharge (n = 111)**
Bisphosphonates	6	11	24	27
alendronate	4	6	13	11
risedronate	0	0	1	1
etidronate	0	0	2	2
pamidronate	3	5	5	7
zolendronate	0	0	3	5
calcitriol	17	19	15	15
calcium	5	12	19	22
hormone replacement therapy	5	8	14	14
vitamin D	3	6	11	17
raloxifene	2	2	1	1
anabolic steroids	1	2	2	2

Table 62 Dispensing of osteoporosis preventive therapy and prednisolone under the PBS and RPBS in Tasmania for March-August 2001 & 2002. The intervention region was southern Tasmania (postcodes 7000-7199), while the control region comprised the North/North-East (postcodes 7200-7299) of the State

Period	Region	DDDs ('000)		Ratio osteoporosis preventive agents:prednisolone
		Osteoporosis preventive agents[a]	Prednisolone	
March - August 2001	Intervention	231	380	0.61
	Control	141	243	0.58
March - August 2002	Intervention	396	402	0.99
	Control	186	245	0.76

[a]alendronate (DDD = 10mg), risedronate (DDD = 5mg), etidronate (DDD = 0.4mg), raloxifene (DDD = 60mg), calcium carbonate (DDD = 3g), calcitriol (DDD = 1mcg), prednisolone (DDD = 10mg)

Chapter 4: Discussion

In this project, written educational material and the technique of academic detailing were employed to promote the use of osteoporosis preventive therapy in patients taking oral corticosteroids. Success of the educational programme was indicated by a statistically significant increase in the prescribing of osteoporosis preventive drugs, relative to prednisolone, in the intervention region compared with the control region. In addition, there was a significant increase in the use of osteoporosis preventive drugs in two well-matched series of patients admitted to hospital and taking long-term oral corticosteroids.

It was apparent that there was a trend to an increase in the use of osteoporosis preventive drugs relative to prednisolone in the control region of the State over the course of the study. This result was not unexpected. The issue of osteoporosis has received considerable government attention and coverage in professional journals and the media over the past two years. Also, contamination of the two groups of prescribers via professional contact is possible, particularly on an island like Tasmania. Nevertheless, our programme was able to achieve significant changes in prescriber behaviour despite this background change. An improvement in prescribing practices within the control region has been previously reported by others and ourselves in academic detailing studies[712-715].

It was evident that the use of bisphosphonates, calcium and vitamin D increased significantly following the programme. There was a significant (4-fold) increase in the use of bisphosphonates following the intervention, in particular alendronate. Current recommendations suggest that bisphosphonates are first-line therapy in the treatment and prevention of corticosteroid-induced osteoporosis[622, 630, 631]. The increase in use of calcium and vitamin D was pleasing as this was one of the key messages of the

programme, and these agents have consistently been shown to be under-utilised in studies investigating the use of preventive therapy in patients prescribed corticosteroids[52, 691].

This programme employed the key strategies for the successful implementation of evidence-based guidelines, as suggested by Gibson[716] the use of guidelines that are well supported by evidence (e.g. from National Osteoporosis Society UK, Osteoporosis Australia and the American College of Rheumatology); local adaptation and consensus, with guidelines being reviewed by local experts; wide dissemination (with the academic detailing programme targeting both general partitioners and pharmacists); and multi-faceted intervention (e.g. with the academic detailing programme being supported by the use of the refrigerator magnet to target patients). The sources of greatest practical importance when attempting to modify prescribing practices are those involving the transfer of information through the medium of personal contact[705, 717]. While academic detailing has previously been shown to be an effective method to modify prescribing behaviour, especially when combined with other approaches[703, 704], this is the first project to our knowledge that has demonstrated that academic detailing can increase the use of osteoporosis preventive therapy in patients prescribed long-term oral corticosteroids.

A recent editorial[718] that focussed on *this* study, highlighted the suboptimal prevention of corticosteroid-induced osteoporosis and acknowledged that an educational outreach is an excellent first step to improve the management of this significant health problem. The authors of the editorial noted that although the results were encouraging, questions about sustainability, generalisation to other health care systems, cost effectiveness, and effect on clinically meaningful outcomes must be answered. In addition, the authors also stated that robust study design and clinical endpoints are

important for influencing widespread policy change. In order to show an impact of reducing fractures from conducting an educational intervention, a very large sample area would be required and studied for a period of time. This is clearly not possible in Tasmania and would require a multi-centre trial with a very robust study design to show a clinical effect from the interventions.

Previous authors have suggested that broad educational effort directed to physicians of varied specialties is needed to ensure that osteoporosis prevention becomes the standard of care for patients receiving long-term corticosteroid treatment[687]. However, it is not only physicians who have contact with patients on long-term corticosteroids. Hart concluded[691] that osteoporosis prophylaxis during corticosteroid treatment should be promoted by local hospital guidelines, hospital and community pharmacists, audit, and GPs. It is imperative to involve other health professionals, such as pharmacists, from the beginning when disseminating clinical guidelines and attempting to change practice[719]. Pharmacists are an ideally placed health professional to offer advice to patients, as they have high levels of patient contact and they are a well respected and highly regarded source of information.

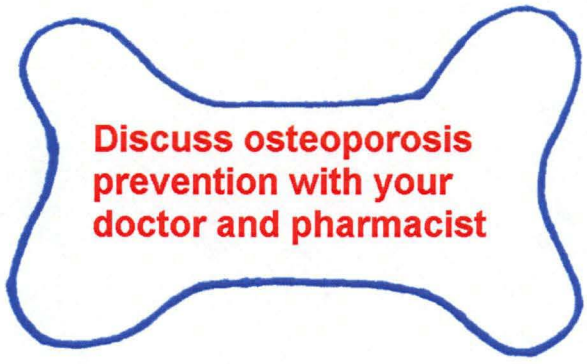
This comprehensive multi-faceted educational intervention has had a significant impact on the prescribing of agents that reduce bone loss and subsequent risk of osteoporosis in patients prescribed long-term corticosteroids. However, there was still clearly room for improvement. For instance, according to our hospital-based data, almost one-half of patients on long-term oral corticosteroids were still not receiving preventive therapy against osteoporosis following the programme. The reasons for this are probably complex, including patient-, physician-, and health care system-related barriers[690]. It has only been recently that proven pharmacological options, such as the bisphosphonates and raloxifene, have become available. Because of their relatively high

cost, the use of bisphosphonates at a subsidised rate in Australia is restricted to patients who have sustained a low-trauma fracture, even if they have documented osteoporosis, while raloxifene has not been approved for the treatment or prevention of corticosteroid-induced osteoporosis. Hence, many patients at high risk of low trauma fracture (e.g. a T-score < -2.5) cannot access these medications, unless they pay the full cost of the therapy.

There are limitations to our study. It is uncertain if the effects from the intervention will be of a long-term nature. It is also unknown whether the hospital patients who were not receiving preventive therapy were considered for possible therapy by their doctor or indeed whether discussions occurred with the patient or if the patient refused any preventive therapy offered. Our results also do not indicate whether patients were receiving any of the medications for osteoporosis prevention or other indication (e.g. HRT for menopausal symptoms, bisphosphonates for Paget's disease), although the use of a control region in the analysis of the prescription data would diminish this possibility. In order to minimise any bias from the PBS and RPBS data, we used ratio indicators as these have been suggested to be more robust, and may describe more valid prescribing measures than prescribing rates[720].

In the future there may be corticosteroids available that suppress immune function without causing bone loss[386]. Until then, ongoing promotion of corticosteroid-induced osteoporosis is imperative for patients receiving these medications if there is to be an impact on reducing the burden of osteoporotic fractures in society. A further method that could be utilised for pharmacists to increase patient awareness maybe through the attachment of an ancillary label to each container of corticosteroid that is dispensed as shown in the example below (Figure 47).

Figure 47 Label that could be affixed to each prescription of corticosteroid dispensed by a pharmacist.



Chapter 5: Conclusion

A multi-faceted educational programme, incorporating academic detailing of GPs and community pharmacists, increased the use of effective osteoporosis prevention strategies in long-term oral corticosteroid users. Written feedback from GPs and pharmacists who participated in the detailing was extremely positive.

General discussion

> *"Despite increasing attention to geriatric pharmacotherapy, there is an enormous need for additional research to improve the use of medications among older adults. The necessary research agenda encompasses much more than just the discovery of new drugs; better use of the current pharmacopeia has great potential to improve the lives of older adult"*[721].

A critical review of the literature on evidence relating to community pharmacy involvement in health development concluded that there is clear potential for pharmacists to contribute to health development. However, it was noted that pharmacists tend to take a reactive rather than proactive approach to health development[722]. The overall aim of this thesis was to assess a pharmacist taking a more proactive role in the medication management of (generally) older community patients to improve the QUM. Figure 3 (page 28) diagrammatically represents the three separate, yet broadly related, parts of this thesis that aimed to improve the QUM. Each part provides an example of the importance pharmacists have in the overall management of medications.

The first intervention (Part I) examined the potential benefit of a pharmacist visiting patients in their home following hospitalisation, to identify and attempt to solve any drug-related issues. This intervention demonstrated that patients who were visited had a reduction in drug-related issues 3 months post-discharge and, importantly, there appeared to be a reduction in re-admission to hospital. Larger studies are required to confirm this finding. Furthermore, a cost-analysis demonstrated that such an intervention, if undertaken on a full-time basis, could save $Aust 150,000 per annum in

the study hospital. This is the first study published demonstrating a reduction in readmission in medical patients following a single visit from a pharmacist only. It is suggested that a home-visit by a pharmacist shortly after discharge is routinely considered in all high-risk patients (e.g., elderly, multiple or changes to medications, multiple comorbidities) discharged from hospital.

Many women (and men) do not receive investigation for osteoporosis and many do not receive treatment after fracture. As stated by Melton recently on the devastation and consequences of osteoporosis[217],

> *"more cost-effective screening and public health interventions with better population penetration and compliance must be developed and validated."*

The second intervention (Part IIa) focussed on the underdetection and therefore undertreatment of osteoporosis by utilising a heel ultrasound machine to screen elderly women. As described by Strong *et al*[723] in a report on the health of rural Australians, access difficulties due to distance, time, cost and transport availability in rural and remote regions are amplified by the shortages and uneven distribution of health facilities and health professionals. Work described in this thesis has shown that community pharmacies may be an ideal place to conduct osteoporosis screenings where access to diagnostic equipment is limited or non-existent, although cost-effectiveness remains controversial. The intervention demonstrated that many women consult their GP following an osteoporosis screening and a significant number make lifestyle changes and/or commence medication to prevent bone loss and reduce their risk of fracture.

This is the first research conducted in Australia demonstrating the effect of QUS screening in community pharmacies on patient self-reported behaviours, medication use

and positive change in women's knowledge of osteoporosis following such an intervention. It is also the first research to apply a revised classification of the WHO criteria for osteoporosis in the community setting. If osteoporosis screening is to occur in community pharmacies, clear guidelines and appropriate training have to be provided to the participating pharmacists. It is critical that pharmacists become more proactive in the screening of osteoporosis and refer subjects who appear to be at risk to their GP, as current practices do not appear to be working. As stated by Melton[217]

> *"The alternative approach is to do nothing while promoting essentially nonexistent public health measures. This is unacceptable because the number of elderly individuals is rising rapidly and something must be done to reduce the personal and societal devastation that will follow in the wake of the corresponding increase in osteoporotic fractures."*

The final intervention (Part IIb) concentrated on the undertreatment of osteoporosis in patients prescribed long-term corticosteroids. Many studies locally and internationally have shown that long-term users of corticosteroids do not receive adequate osteoporosis prevention and, importantly, there has been a little evidence of interventions to improve this situation. Work described in this thesis demonstrated, with both local hospital data and community prescribing data, that there was a significant change in the use of osteoporosis preventive agents in users of corticosteroids following a multi-faceted intervention. This is the first research, to our knowledge, to show an improvement in the use of osteoporosis preventive agents in patients prescribed long-term corticosteroids. Further research is required to evaluate long-term changes.

This study (Part IIb) did not include a formal economic analysis, although it is likely that the cost of these types of educational interventions targeting GPs would be small in comparison to the costs associated with osteoporotic fractures. There is some evidence that academic detailing can be cost-effective in influencing prescribing behaviour[724].

In conclusion, work described in this thesis has conclusively shown the various useful roles a pharmacist can fulfil to improve the QUM among community-dwelling patients. Overall, GPs, pharmacists and patients found each of the interventions useful. It is now up to community pharmacists to determine whether or not they choose to embrace the possibilities available to them to promote pharmaceutical care and improve patient outcomes. As recently stated by Bobb[725] on reducing prescribing errors,

> *"Pharmacist involvement... is vital for achieving maximum medication safety."*

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